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METHODS FOR PREVENTING OR ATTENUATING PATHOANGIOGENIC CONDITIONS

Abstract:

Abstract of WO0156598

Methods are provided for preventing or attenuating pathoangiogenic conditions by administering at least one GBS toxin receptor polypeptide or at least one immunogenic fragment thereof. Also provided are a composition that includes a GBS toxin receptor polypeptide and a method for making such a composition. In ano fdb ther embodiment of the invention, immunized animals also receive GBS toxin, immunocompatible antibodies to the GBS toxin receptor, and/or expanded autologous T cells to the GBS toxin receptor. Also included in this invention are methods of identifying additional GBS toxin receptors.

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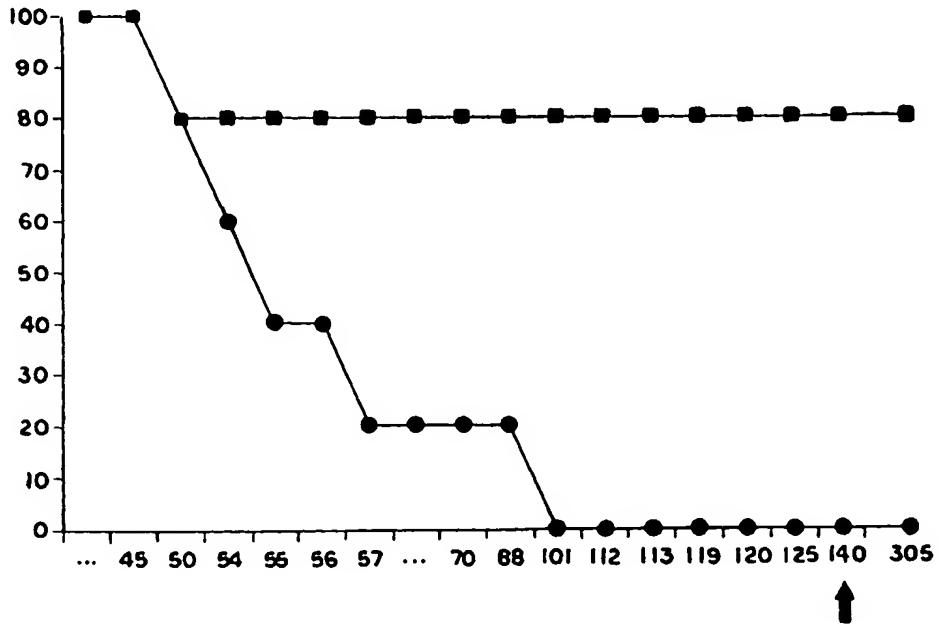

(57) Abstract: Methods are provided for preventing or attenuating pathoangiogenic conditions by administering at least one GBS toxin receptor polypeptide or at least one immunogenic fragment thereof. Also provided are a composition that includes a GBS toxin receptor polypeptide and a method for making such a composition. In another embodiment of the invention, immunized animals also receive GBS toxin, immunocompatible antibodies to the GBS toxin receptor, and/or expanded autologous T cells to the GBS toxin receptor. Also included in this invention are methods of identifying additional GBS toxin receptors.

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METHODS FOR PREVENTING OR ATTENUATING PATHOANGIOGENIC CONDITIONS

TECHNICAL FIELD

This invention provides methods and compositions for preventing or ameliorating medical conditions arising from the formation of pathological neovasculature. These conditions include cancer, scarring during wound healing, keloid formation, chronic wounds, gliosis during repair of nerve injury, reperfusion injury, rheumatoid arthritis, psoriasis and atherosclerosis.

BACKGROUND

Cancer is the second leading cause of death in the United States, second only to heart disease (which is frequently due in part to atherosclerosis). Since 1990 approximately 12 million new cases of cancer have been diagnosed and five million persons have died of cancer in the United States.

Neural injury can result in death or profound disability such as loss of movement, impaired sensory perception, loss of cognitive functions, seizures, and emotional and personality disorders.

Rheumatoid arthritis (RA) and psoriasis are prevalent chronic inflammatory diseases propagated by inflammatory angiogenesis. RA affects approximately 1-2% of the world's population. RA sufferers often experience pain and impaired mobility, and as a group they have twice the mortality rate of their unaffected counterparts. Approximately 1-3% of United States residents and an even higher percentage of Northern Europeans suffer from psoriasis, a disease in which the skin develops recurrent erythematous plaques that burn and itch.

Chronic wounds or skin ulcers are major problems in diabetic and geriatric populations. Poor healing of acute wounds inflicted by accidents or surgical incisions and the formation of wound-associated scars seriously impair recovery from such events. Reperfusion injuries cause damage to transplanted organs as well as tissues near the site of surgical intervention, stroke or heart attack.

There is a need for a prophylaxis that would prevent cancer, gliosis during repair of nerve injury, chronic inflammatory diseases such as rheumatoid arthritis and psoriasis, scarring during wound healing, keloid formation, chronic wounds, reperfusion injury and atherosclerosis. There is also a need for an effective and safe therapy for each of these medical conditions.

SUMMARY OF THE INVENTION

The present invention provides a method for preventing or protecting against pathoangiogenic conditions by administering one or more Group B ß-hemolytic *Streptococci* (GBS) toxin receptors or immunogenic fragments thereof to a mammal in an amount sufficient to induce or maintain an immune response to at least one of the GBS toxin receptors.

The present invention also provides a method for decreasing the incidence of, ameliorating, lessening the severity of, or attenuating pathoangiogenic conditions by administering one or more GBS toxin receptors or immunogenic fragments thereof to a mammal in an amount sufficient to induce or maintain an immune response to at least one of the GBS toxin receptors.

Another aspect of the present invention is a vaccine comprising one or more GBS toxin receptors or immunogenic fragments thereof in combination with a pharmaceutically acceptable excipient.

The pathoangiogenic conditions that can be prevented or attenuated by the methods and compositions of the present invention include cancer, scarring during wound healing, keloid formation, chronic wounds, gliosis during repair of nerve injury, reperfusion injury, rheumatoid arthritis, psoriasis and atherosclerosis.

Preferred GBS toxin receptors are HP59 and SP55 and substantially identical variants thereof. Mammals treated with the methods or the compositions of the present invention may be additionally treated with GBS toxin, with immunocompatible antibodies directed at the GBS toxin receptor, or with autologous activated GBS toxin receptor-recognizing T cells.

Yet another aspect of the present invention is a method for making a composition for the treatment and/or prevention of pathoangiogenic conditions. This method involves providing one or more GBS toxin receptors or immunogenic fragments thereof, and formulating it in a pharmaceutically acceptable excipient. An adjuvant may optionally be provided.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 presents growth curves for Lewis Lung tumors in control mammals and in male and female mammals immunized with a composition of the present invention. The y-axis represents tumor volume and the x-axis represents the day the tumor volume was measured. Male controls are denoted by blackened diamonds, female controls are denoted by blackened circles; male immunized are denoted by clear circles and female immunized are denoted by clear diamonds.

Fig. 2 presents survival curves for female mammals immunized with a composition of the present invention and challenged intravenously with melanoma cells and for female control mammals equally challenged but not immunized. The y-axis represents percentage of survivors and the x-axis represents the number of days of survival. The blackened circles denote female controls and the blackened squares denote female immunized mammals.

DESCRIPTION OF SPECIFIC EMBODIMENTS

INTRODUCTION

Group B ß-hemolytic *Streptococci* (GBS) are ubiquitous microorganisms that are generally harmless to humans with one exception – newborn infants infected with GBS frequently develop GBS pneumonia (also called "early onset disease" or "early onset septicemia"), a disease that is associated with high morbidity and mortality. Hellerqvist and colleagues identified a polysaccharide GBS toxin that is a major factor in the complications of GBS pneumonia (Hellerqvist, C.G. *et al., Pediatr. Res.,* 12:892-898 (1981); Sundell, H. *et al., J. Pediatr.* 137: 338-344 (2000)).

GBS toxin was subsequently found to have many therapeutic properties. It is an anticancer agent that inhibits vascularization of solid tumors (U.S. Patent No. 5,010,062 and corresponding European Patent No. EP 0 445 280 B1; DeVore *et al.* (1997) *Clinical Cancer Res.* 3,365-372)). In addition, as described in U.S. Patent No. 5,858,991 and WO98/32453, GBS toxin facilitates wound healing in mammals by minimizing scarring and accelerating healing, and reduces wound-related tumor progression. GBS toxin also enhances repair of neural injuries by minimizing the formation of glial scars (U.S. Patent No. 5,981,508 and WO98/32448) and ameliorates the symptoms of certain chronic inflammatory diseases such as rheumatoid arthritis and psoriasis (WO98/32452).

GBS toxin's anticancer effect has been traced to its ability to rapidly bind tumor-associated endothelial cells and to subsequently activate complement by the alternate (C3) pathway. Activated leukocytes soon infiltrate the endothelial cells, which are subsequently destroyed, and the tumors shrink as a result of the inflammatory response and insufficient blood supply (Yan *et al., Angiogenesis* 2:219-233 (1998); Wamil, B.D. *et al., AACR Proceedings,* 38:237 (1997)).

Without limitation to a particular theory, it is believed that GBS toxin's other therapeutic effects are due to a similar mechanism. Nerve trauma, wounds, disruption of blood flow, reperfusion, atherosclerotic plaques, rheumatoid arthritis and psoriasis all induce hypoxia which in turn causes the release of vascular endothelial growth factor (VEGF) (Liu *et al.*, J. *Neuroscience* 17:5395-5406 (1997)). VEGF stimulates endothelial cells to dedifferentiate and begin forming new vasculature by a process known as pathological angiogenesis and also known as pathoangiogenesis. In patients with neural injuries, the newly formed vasculature facilitates gliosis, a proliferation of glial cells which gives rise to glial scars that sterically interfere with re-establishment of neuronal connectivity. Neovasculature in the joints of rheumatoid arthritis sufferers facilitates synovial tissue hyperplasia, pannus formation, and cartilage destruction. Similarly, pathological angiogenesis facilitates the establishment, maintenance and enlargement of psoriatic lesions and is a driving force in the formation of granulation tissue, which leads to chronic wounds or scar formation (including keloids) in the vicinity of wounds. In atherosclerosis, the pathological neovasculature provides oxygen and nutrients to smooth muscle and endothelial cells located below plaques and results in further narrowing of affected blood vessels. Other conditions caused by pathological angiogenesis include diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, angiofibromas, immune and non-immune inflammation, hemangiomas, Kaposis' sarcoma, and endometriosis (see PCT Publication Number WO 91/10424, page 13, lines 14-21). Additional conditions caused by pathological angiogenesis include corneal graft neovascularization, ocular tumors, trachoma, and hemophiliac joints (see European Patent Application Publication Number EP 0 325 199 A2, page 2, lines 12-19). Additional conditions cuased by pathological angiogenesis include reinopathy of prematurity, macular degeneration, Behcet's syndrome, Osler-Weber-Rendu disease, osteoarthritis, corneal graft rejection and ocular neovascular diseases (see PCT Publication Number WO 94/20085, page 2, line 27 to page 6, line 14). GBS toxin interferes with these harmful processes by binding to the budding pathological neovasculature and targeting it for destruction by the immune system.

It was believed that GBS toxin attacks the lungs of human neonates and binds embryonic neovasculature via receptors present on these tissues at birth and for a short time (about 7 days in term babies and longer in premature infants) thereafter. It was further hypothesized that the same receptors are present later in life only upon pathological neovasculature (i.e. new capillaries formed by pathological angiogenesis). This belief has been confirmed by the recent identification of novel proteins found on such cells that specifically bind GBS toxin. The nucleic acid and amino acid sequences of the human GBS toxin receptor known as HP59 are shown in SEQ ID NO:1 and SEQ ID NO:2, respectively (GenBank Accession Number AF244578). The nucleic acid and amino acid sequences of the sheep GBS toxin receptor known as SP55 (cloned from a sheep lung library, GenBank Accession Number AF244578) are shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. Both HP59 and SP55 are integral proteins with multiple transmembrane domains. Each has several putative sites for phosphorylation by cAMP-dependent kinase, protein kinase C (PKC) and casein kinase II (CK2) as well as putative sites for glycosylation and myristylation. Although HP59 has 41 amino acids at its amino terminus that SP55 lacks, the two proteins are otherwise 87% identical.

As expected, GBS toxin receptor is expressed on the lungs of human neonates and sheep (which are susceptible to infection by GBS). It is not expressed in the vasculature associated with normal (healthy, non-neonate) human ovary, colon, breast or lung tissue, but it is present in the vasculature of tumors in these tissues. Thus, GBS toxin receptor expression is correlated with medical conditions involving pathologic angiogenesis and the receptor is not seen in healthy tissue from humans who are more than one month old (except for premature babies, in which expression is correlated with their due dates).

Although not wishing to be bound by theory, it is believed that since the GBS toxin receptor is present on the pathological neovasculature associated with pathoangiogenic conditions, the immune system, if primed to recognize the GBS toxin receptor, will attack such forming vasculature and the pathoangiogenic condition will be prevented or attenuated. Therefore, the present invention involves methods and compositions for invoking an immune response to the GBS toxin receptor.

DEFINITIONS

Generally, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The nomenclature used herein and the laboratory procedures in immunology, cell culture,

biochemistry and molecular biology described below are those well known and commonly employed in the art. Standard techniques are used for recombinant nucleic acid methods, polypeptide synthesis, and production of monoclonal and polyclonal antibodies. Enzymatic reactions and purification steps supplied by manufacturers are typically performed according to the manufacturer's specifications. The techniques and procedures are generally performed according to conventional methods in the art and various general references (*See* generally, Sambrook *et al., Molecular Cloning: A Laboratory Manual*, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.) which are provided throughout this document. The nomenclature used herein and the laboratory procedures in analytical chemistry, organic synthetic chemistry, immunology and pharmaceutical formulation described below are those well known and commonly employed in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical formulation and delivery, and treatment of mammals. As employed throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

For the purposes of this invention, the term "GBS toxin" means any purified fraction or component of the natural GBS toxin, or derived from media or protease digests of lysed GBS bacterial; and whose toxicity can be confirmed by either of the following specified assay procedures. The potency of isolated GBS toxin as a tumor growth inhibitor may be ascertained by peroxidase-antiperoxidase (PAP) assays of tumor tissue specimens using anti-GBS toxin IgG, and by infusion in a sheep model at 2 μgs 10^{-11} moles per kg (Hellerqvist, C.G. *et al.,* 1981, cited above; Hellerqvist, C.G. *et al. PNAS* 84:51-56 (1987)).

"GBS toxin receptor" means a proteinaceous molecule capable of binding a toxin from Group B β-hemolytic *Streptococcus* bacteria (GBS toxin). A GBS toxin receptor is usually found in nature on the surface of a cell. Recombinant membrane-bound and soluble GBS toxin receptors can be produced by laboratory techniques known in the art. GBS toxin receptor refers to any receptor that interacts with a GBS toxin as defined herein.

As used herein, a vaccine or method is said to "prevent" or "protect against" a medical condition if its administration to an individual results in the failure of the individual to develop the medical condition.

As used herein, a vaccine or method is said to "ameliorate," "attenuate" or "lessen the severity of" a medical condition if its administration to an individual results either in the suppression or partial suppression of at least one symptom or other manifestation of the medical condition in the individual.

As used herein, a vaccine or method is said to "decrease the incidence of" a medical condition if its administration to an individual has the effect of decreasing the probability that the individual will develop the medical condition.

A "pathoangiogenic condition" is any medical condition associated with pathological angiogenesis such as that caused by for instance the hypoxia-induced, VEGF-mediated formation of new vasculature from dedifferentiated endothelial cells. Pathological angiogenesis occurs in such diseases as diabetic retinopathy, hemangioma, cancer, psoriasis, RA, osteoarthritis and atherosclerosis. (Folkman *et al., Science*, 235:442 (1987); Kimball *et al., Agents & Actions,* 34:329 (1991)). It is also is associated with the formation of glial scars in the vicinity of injured nerves and in the formation of keloids, reperfusion injuries and scars during wound healing. Pathological angiogenesis is distinct from physiological neovascularization, a basic repair mechanism that occurs under normal, healthy circumstances (such as wound healing, the female menstrual cycle, and pregnancy) and is believed to result from the proliferation of *existing* endothelial cells after the disruption of contact inhibition (Brem & Folkman, *J. Ped. Surg.*, 28:445 (1993)).

An "immune response" may be humoral or cell-mediated or both. In a humoral response, the immunized animal produces antibodies that recognize and specifically bind a particular antigen. Preferably, the titer for such antibodies would be at least about 1:200 as measured by ELISA. A cell-mediated immune response is characterized by the presence of helper T cells, suppressor T cells, and/or cytotoxic T cells that recognize the antigen. The presence of such cells can be confirmed by methods known in the art, including the development of a raised area of at least 1mm within 72 hours after the subcutaneous administration of a sample of the antigen.

As used in the context of an antibody administered to a mammal, such an antibody is "immunocompatible" with such mammal if the mammal's immune system does not treat it as a foreign protein and mount an immune response against it. The antibody to be administered may be obtained from a mammal of the same species as the recipient mammal. Alternatively, such antibody can be engineered to contain constant regions that resemble those of antibodies naturally produced by the recipient mammal. Where the recipient mammal is a human, such antibodies are frequently referred to as "humanized" antibodies.

The term "immunogenic" means having antigenic properties or being capable of being specifically bound by an antibody that can specifically bind the antigen. A substance has antigenic properties if it can generate or is capable of eliciting an immune response when

administered to an animal under conditions known in the art to facilitate the production of antibodies and/or T cells that will recognize and elicit a cytotoxic response toward cells expressing the particular antigen.

The term "adjuvant" refers to an agent used to enhance the immune response of an immunized mammal to an antigen.

The term "parenteral" as used herein includes subcutaneous injections, intraperitoneal or intramuscular injection, or infusion techniques.

The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, analogs, or glycosylated, phosphorylated or myristylated isoforms of a polypeptide sequence. Hence, native protein, fragments, analogs and glycosylated, phosphorylated and myristylated isoforms are species of the polypeptide genus.

The term "isolated" as used herein in the context of a polypeptide means a polypeptide that is no longer associated with the cell that the polypeptide is normally associated with in nature in the same manner as it is normally associated in nature, such as (1) a polypeptide free of at least some other polypeptides from the same source, (2) a polypeptide expressed by a cell from a different species, (3) a polypeptide that does not occur in nature, and (4) a polypeptide produced from cDNA, recombinant RNA, or synthetic origin or some combination thereof.

The term "naturally occurring" means found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) found in nature and which has not been intentionally modified in the laboratory is naturally occurring.

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned by the BLAST computer program, share at least about 80 percent sequence identity, at least about 86 percent sequence identity, and preferably at least about 90 percent sequence identity. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of about 10 or less are preferred, with about 5 or less being more preferred. Residue positions which are not identical may differ by conservative amino acid substitutions. Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side

chains is lysine, arginine, and histidine; and a group of amino acids having sulfur-containing side chains is cysteine and methionine.

The term "fragment" as used herein refers to a peptide that has an amino-terminal, internal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally occurring sequence deduced, for example, from a full-length DNA sequence. Fragments typically are at least about 3 amino acids long, preferably are about 5-10 amino acids long, more preferably are about 10-50 amino acids long, and even more preferably are more than about 50 amino acids long. Also preferred are fragments that comprise one or more extracellular domains of a GBS toxin receptor. Such fragments may also comprise portions of transmembrane and intracellular domains sufficient to maintain the polypeptide fragment in a stereochemical conformation on the surface of a cell, lipid membrane, liposome, micelle, or other lipophilic structure.

The singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The SEQ ID NOs of the nucleic acid and amino acid sequences described herein are summarized below in Table 1.

Table 1 -- Nucleic Acid and Amino Acid Sequences

SEQ ID NO:	Type of Sequence	Description
SEQ ID NO:1	Nucleic acid	Full-length human GBS toxin receptor (HP59)
SEQ ID NO:2	Amino acid	Full-length human GBS toxin receptor (HP59)
SEQ ID NO:3	Nucleic acid	Sheep GBS toxin receptor (SP55)
SEQ ID NO:4	Amino acid	Sheep GBS toxin receptor (SP55)

The headings provided herein describe the general topic discussed and are not intended to be exclusive of information discussed in other sections. Frequently, information, methods, compositions, and other aspects may be applicable to more than one embodiment of the invention and can be so combined.

One aspect of the present invention is a method for preventing a pathoangiogenic condition in a mammal by administering to the mammal an amount of one or more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain in the mammal an immune response to at least one of the GBS toxin receptors.

Another aspect of the present invention is a method for attenuating a pathoangiogenic condition in a mammal by administering to the mammal an amount of one or

more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain in the mammal an immune response to at least one of the GBS toxin receptors. This method may be performed at a time when the mammal does not have any symptoms of the pathoangiogenic condition. Such administration serves to lessen the severity or progression of the subsequently developed pathoangiogenic condition. When the method is performed on a mammal suffering from the pathoangiogenic condition, it will ameliorate one or more symptoms of the pathoangiogenic condition.

The aforementioned methods may be performed on any animal that expresses a GBS toxin receptor on pathological neovasculature. Preferably, such animal is a mammal that does not express the receptor on healthy tissues. It is known that human embryos and full-term newborn babies up to about 10 days old have GBS toxin receptors on their lung vasculature. Sheep, cows and cats express GBS toxin receptors on their lung vasculature shortly after birth and thereafter. Preferred recipients of this method are full-term humans older than ten days, dogs, mice, pigs, goats and horses.

In other embodiments of the invention, immunized animals receive antibodies to GBS toxin receptor or immunogenic fragments thereof, or expanded autologous T cells to GBS toxin receptor, or combinations thereof. These methods may be used to attack the vasculature in pathoangiogenic conditions. These embodiments may be used independently of each other, or in combination with the treatments disclosed herein for pathoangiogenic diseases, or in combination with other treatments for pathoangiogenic diseases used in the art.

For example, as stated earlier, it was believed that GBS toxin attacks the lungs of human neonates and binds embryonic neovasculature via receptors present on these tissues at birth. GBS toxin was subsequently found to inhibit vascularization of solid tumors and ameliorate the symptoms of other diseases. Therefore, in another embodiment of the invention, in addition to receiving at least one GBS toxin receptor or at least one immunogenic fragment thereof, immunized animals also receive GBS toxin or fragments thereof, antibodies to at least one GBS toxin receptor or immunogenic fragments thereof, or expanded autologous T cells or combinations thereof. The supplemental treatments are preferred when the animal is at high risk for or is currently suffering from a pathoangiogenic condition. GBS toxin may be obtained from CarboMed, Inc. (Brentwood, TN) or may be purified as taught in U.S. Patent Nos. 5,010,062 and 5, 811,403 and WO98/14603, which are hereby incorporated by reference. For human recipients, GBS toxin is preferably administered in amounts in the range of about 5μg/kg to about 25μg/kg. Methods for administering GBS toxin for the treatment of the following

pathoangiogenic conditions are taught in the following patents which are herein incorporated by reference:

Condition(s)	Patent
Cancer	U.S. 5,010,062
Scarring	U.S. 5,858,991
Keloids	U.S. 5,858,991
Reperfusion injury	U.S. 5,858,991
Atherosclerosis	U.S. 5,858,991
Burns	U.S. 5,858,991
Chronic wounds	U.S. 5,858,991
Gliosis	U.S. 5,981,508
Rheumatoid arthritis	WO98/32452
Psoriasis	WO98/32452

Antibodies to the GBS toxin receptor can be obtained by immunizing animals including rabbits, mice, goats and chickens with the GBS toxin receptor or an immunogenic fragment thereof. Monoclonal antibodies, polyclonal antibodies and variants thereof can be used. Examples of variants include, but are not limited to, single-chain (recombinant) antibodies, "humanized" chimeric antibodies, and immunologically active fragments of antibodies (e.g., Fab and Fab' fragments). The production of non-human monoclonal antibodies, e.g., murine, is well known (see, e.g., Harlow *et al.*, *Antibodies A Laboratory Manual*, Cold Spring Harbor Press, pp. 139-240, 1989). Immunocompatible antibodies are preferred to prevent the immunized animal from mounting an immune response to the GBS toxin receptor antibodies. To prepare antibodies that are immunocompatible to a human, it is desirable to transfer antigen binding regions of non-human monoclonal antibodies, e.g. the $F(ab')_2$ or hypervariable regions of murine monoclonal antibodies, to human constant regions (Fc) or framework regions by recombinant DNA techniques to produce substantially human molecules. Such methods are generally known and are described in, e.g., U.S. Pat. Nos. 4,816,397 and 4,946,778, and EP publications 173,494 and 239,400. Alternatively, one may isolate DNA sequences which code for a human monoclonal antibody or portions thereof that specifically bind to the receptor protein by screening a DNA library from human B cells according to the general protocol outlined in WO 90/14430, and then cloning and amplifying the sequences which encode the antibody (or binding fragment) of the desired specificity. These sequences may be inserted into the DNA of a

mammal in such a manner that the mammal will secrete the antibodies into its milk (Genzyme Transgenics, Framingham, MA). Such antibodies may be administered intraperitoneally or intravenously. Alternate regimens can be determined by one of skill in the art using the basic principles discussed under "Administration" below.

The antibodies can also be used to develop a method of targeting a cytotoxic agent for delivery to a cell that expresses a GBS toxin receptor. For example, a cytotoxic agent can be coupled to an antibody that binds a GBS toxin receptor for selective delivery to the neovasculature of a growing tumor. Such a delivery system would permit a highly concentrated, localized attack on a growing tumor, while minimizing the adverse systemic side effects encountered with most chemotherapeutics.

The sections that follow address in greater detail the selection of immunogenic fragments of the GBS toxin receptor, the production of the receptor polypeptide, identification of other GBS toxin receptors, composition preparations, vaccine preparations, pharmaceutical compositions, administration of the compositions or vaccines, and monitoring of immune response.

IMMUNOGENIC PEPTIDES OF THE GBS TOXIN RECEPTOR

One embodiment of the present invention involves the administration of one or more immunogenic fragments of a GBS toxin receptor. Preferred receptors are HP59 and SP55 and preferred fragments include the Hab1, Hab2 and Hab3 peptides shown in Table 3 and used in Example 1. Preferably the mammal receives a combination of at least two immunogenic fragments and more preferably all three such fragments. Co-administration of fragments from HP59 and SP55 may be desirable to elicit a robust immune response. The immunogenic fragments may contain naturally occurring post-translation modifications such as glycosylation, myristylation or phosphorylation. Other immunogenic fragments of a GBS toxin receptor may be administered in the present invention and one of skill in the art can readily identify appropriate fragments using techniques known in the art.

A number of methods has been developed to predict the location of immunogenically important epitopes on proteins. The outcome of the combined predictions gives a good forecast of antigenic sites. Suitable GBS toxin receptor fragments may be selected, for instance, from the most hydrophilic parts of the receptor, e.g. by applying the technique described by Hopp and Woods (T. P. Hopp and K. R. Woods (1981): *Proc. Natl. Acad. Sci, U.S.A.* 78, 3824-3828). Another suitable method for selecting immunogenic fragments is

described by Chou and Fasman (P. Y. Chou and G. D. Fasman (1987) *Advances in Enzymology* 47, 45-148). Various additional algorithms can be used to predict the antigenically important regions of the GBS toxin receptor, such as a prediction of the flexibility of the polypeptide chain (P. A. Karplus and G. E. Schultz, 1985, *Naturwissenschaften* 72, 212-213), a beta-turn probability profile (P. Y. Chou and G. D. Fasman, 1979, *Biophys. J.* 26, 367-385), the probability profiles in the 3 conformations for the sequence (Gascuel, O. and J. L. Golmard, 1988, *CABIOS* 4, 357-365), a prediction of the secondary structure of the sequence (J. Novotny and C. Auffray, 1984, *Nucleic Acids Research* 12, 243-255). Additional information on the location of relevant epitopes can be obtained using the PEPSCAN-method, developed by Geysen and Meloen (H. M. Geysen, R. H. Meloen and S. J. Barteling (1984) *Proc. Natl. Acad. Sci., U.S.A.* 81(13); 3998-4002). All of these techniques can be used to select suitable GBS toxin receptor fragments for use as immunogenic antigens in the present invention.

In addition, immunoreactive epitopes of the GBS toxin receptor can be identified by expressing DNA fragments from the GBS toxin receptor gene in suitable plasmids, such as the pEX plasmids (K. Stanley and J. P. Luzio, 1984. *EMBO J.* 3, 1429-1434, and J. G. Kusters, E. J. Jager and B. A. M. Van der Zeijst, 1989. *Nucl. Acids Res.*, 17, 8007). In this system, heterologous expression leads to the synthesis of a C-terminal extension of the cro-β-galactosidase hybrid protein. Restriction-endonuclease sites in the GBS toxin receptor DNA sequence can be used to obtain fragments of the GBS toxin receptor gene for insertion into the pEX plasmids. pEX clones synthesizing fusion proteins derived from different overlapping regions of the GBS toxin receptor are then used for further characterization. The GBS toxin receptor fragments are purified, fractionated by polyacrylamide gel electrophoresis, and blotted to nitrocellulose membranes. These membranes are then reacted with polyclonal antibodies directed at the GBS toxin receptor. Only the fragments containing the immuno-reactive epitopes will react with these antibodies. To delineate the minimal length of the epitopes, the DNA inserts of the reactive clones can be progressively shortened by Exonuclease III digestion, or by cloning synthetic oligonucleotides encoding small overlapping parts of the GBS toxin receptor (J. G. Kusters, E. J. Jager, G. Koch, J. A. Lenstra. W. P. A. Posthumus, R. H. Meloen and B. A. M. Van der Zeijst, 1989. *J. Immunol.*, 143, 2692-2698). The epitopes can then be tested for their abilities to generate an immune response in the mammal of choice. Such testing can be performed using methods known in the art as well as methods described in the "Monitoring Immune Response" section of this application.

Using the method of Hopp and Woods via the "Antigen" program in PC/GENE, Hellerqvist and colleagues have identified three regions of SP55, shown below in Table 2, as having high hydrophilicity and as likely to be immunogenic.

Table 2 -- High Points of Hydrophilicity in SP55

No.	Average Hydrophilicity	Sequence
1	2.05	Glu-Glu-Gly-Ser-Asp-Arg (residues 14-19 of SEQ ID NO:4)
2	1.52	Lys-Asp-Asn-Arg-Thr-Ser (residues 75-80 of SEQ ID NO:4)
3	1.33	Arg-Ala-Pro-Arg-Ala-Glu (residues 25-30 of SEQ ID NO:4)

Hellerqvist and colleagues have successfully prepared mouse monoclonal antibodies directed to the portions of HP59 shown in Table 3 and rabbit polyclonal antibodies directed at the peptides from SP55 shown in Table 4. The rabbit polyclonal antibodies bind both SP55 and HP59 and several of the hybridomas produce monoclonal antibodies that recognize both SP55 and HP59.

Table 3 -- Immunogenic Peptides from HP59

Peptide	Amino Acid Sequence	Size	SEQ ID Ref.
Hab1	LARNDGEESTDRTPL	15 aa	residues 49-63 of SEQ ID NO:2
Hab2	NTTLEDNRTSKACP	14 aa	residues 112-125 of SEQ ID NO:2
Hab3	PPRPVQPARPGGFGLSGRRSL	21 aa	residues 8-28 of SEQ ID NO:2
Hab4	LARNDGEESTDRTPLLPGAPR AEAAPVC	28 aa	residues 49-76 of SEQ ID NO:2

Table 4 -- Immunogenic Peptides from SP55

Peptide	Amino Acid Sequence	Size	SEQ ID Ref.
p56a	APSDGEEGSDRTPLLQRAPRAEPAPVC	27 aa	residues 9-35 of SEQ ID NO:4
p55a[1]	LAPSDGEEGSDRTPL	15 aa	residues 8-22 of SEQ ID NO:4
p57a[2]	NTTAKDNRTSYECA	14 aa	residues 71-84 of SEQ ID NO:4

[1]Peptide p55a is a fragment of an extracellular domain of GBS toxin receptor.

[2]Peptide p57a is a fragment of an intracellular domain of GBS toxin receptor.

PREPARATION OF GBS TOXIN RECEPTOR POLYPEPTIDES

The GBS toxin receptor polypeptides of the present invention may be utilized in an unmodified state. Alternatively, the polypeptides may be glycosylated, myristylated, or phosphorylated at one or more of the putative sites for such post-translational modifications. The GBS toxin receptor protein or polypeptides may be prepared as homopolymers (a multitude of identical GBS toxin receptor polypeptides coupled) or heteropolymers (one or more GBS toxin receptor polypeptides coupled to one or more different GBS toxin receptor polypeptides), or may be coupled to one or more other compounds in order to enhance immunogenicity.

In one embodiment of the invention, the GBS toxin receptor protein is naturally occurring and can be isolated from a cell extract by protein purification techniques known in the art, such as, for example, ion exchange column chromatography, high performance liquid chromatography (HPLC), reverse phase HPLC, or affinity chromatography using antibodies that recognize the GBS toxin receptor. The purified protein can be optionally lyophilized and stabilized.

In another embodiment, the GBS toxin receptor or polypeptide fragments from it can be synthesized chemically by techniques well known in the art, such as solid-phase peptide synthesis (Stewart et al., SOLID PHASE PEPTIDE SYNTHESIS, W.H. Freeman Co., San Francisco (1963)); Merrifield, *J. Am. Chem. Soc.* 85:2149-2154 (1963)). These and other methods of peptide synthesis are also exemplified by U.S. Patent Nos. 3,862,925, 3,842,067, 3,972,859, and 4,105,602. The synthesis can use manual synthesis techniques or automatically employ, for example, an Applied BioSystems 430A or 431A Peptide Synthesizer (Foster City, California) following the instructions provided in the instruction manual supplied by the manufacturer.

Alternatively, the polypeptides can be expressed using polynucleotides encoding the polypeptide(s) in operative association with an appropriate control sequence including a promoter in an expression vector suitable for expression, preferably in a mammalian cell, and also in bacterial, insect, or yeast cells. Preferably, the GBS toxin receptor polynucleotide or a fragment thereof can be expressed in a mammalian system. Such expression will usually depend on a mammalian promoter, which is any DNA sequence capable of binding mammalian RNA polymerase and initiating the downstream (3') transcription of a coding sequence (e.g. structural gene) into mRNA. Usually, a promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region typically includes an RNA polymerase binding site and a transcription initiation site.

Vectors suitable for replication in mammalian cells are known in the art, and can include viral replicons, or sequences that ensure integration of the sequence encoding PAK65 into the host genome. Suitable vectors can include, for example, those derived from simian virus SV40, retroviruses, bovine papilloma virus, vaccinia virus, and adenovirus. A suitable vector, for example, is one derived from vaccinia viruses. In this case, the heterologous DNA is inserted into the vaccinia genome. Techniques for the insertion of foreign DNA into the vaccinia virus genome are known in the art, and utilize, for example, homologous recombination. The insertion of the heterologous DNA is generally into a gene that is non-essential in nature, for example, the thymidine kinase gene (tk), which also provides a selectable marker. Plasmid shuttle vectors that greatly facilitate the construction of recombinant viruses have been described (see, for example, Mackett et al. (1984); Chakrabarti et al. (1985); Moss (1987)). Expression of the heterologous polypeptide then occurs in cells or individuals which are immunized with the live recombinant vaccinia virus.

A specific case of the above embodiment is a so-called vector vaccine in which recombinant polynucleotide are produced in the immunized animal via viral vectors. The viruses applicable for this purpose should have the ability to replicate in the animals to be immunized. These viruses, furthermore, should possess a genomic region suitable for insertion of the GBS toxin receptor protein or polypeptide gene. Suitable viruses for this purpose are for example enteral viruses such as certain adeno viruses. A particular application of the present invention is concerned with bacterial vector vaccines in which bacteria capable of colonizing the mammal (e.g. *Salmonella* bacteria) are transformed in order to enable them to express a GBS toxin receptor polypeptide in such a way that it will lead to an immunogenic response against the GBS toxin receptor.

Suitable mammalian expression vectors usually contain one or more eukaryotic transcription units that are capable of facilitating expression in mammalian cells. The transcription unit is comprised of at least a promoter element to mediate transcription of foreign DNA sequences. Suitable promoters for mammalian cells are known in the art and include viral promoters such as those from simian virus 40 (SV40) (Subramani *et al., Mol Cell. Biol.* 1:854–864, 1981), cytomegalovirus (CMV) (Boshart et al., Cell 41:521–530, 1985), Rous sarcoma virus (RSV), adenovirus (ADV) (Kaufman and Sharp, *Mol. Cell. Biol.* 2:1304–1319, 1982), and bovine papilloma virus (BPV), as well as cellular promoters, such as a mouse metallothionein-1 promoter (U.S. Patent No. 4,579,821), a mouse VK promoter (Bergman *et al., Proc. Natl. Acad.*

Sci. USA 81:7041–7045, 1993; Grant *et al., Nuc. Acids Res.* 15:5496, 1987), and a mouse VH promoter (Loh *et al., Cell* 33:85–93, 1983).

The optional presence of an enhancer element (enhancer), combined with the promoter elements described herein, will typically increase expression levels. An enhancer is any regulatory DNA sequence that can stimulate transcription up to 1000-fold when linked to endogenous or heterologous promoters, with synthesis beginning at the normal mRNA start site. Enhancers are also active when they are placed upstream or downstream from the transcription initiation site, in either normal or flipped orientation, or at a distance of more than 1000 nucleotides from the promoter (Maniatis *et al.* (1987) *Science* 236:1237; Alberts *et al.* (1989) MOLECULAR BIOLOGY OF THE CELL, 2nd ed.). Enhancer elements derived from viruses can be particularly useful, because they typically have a broader host range. Examples useful in mammalian cells include the SV40 early gene enhancer (Dijkema *et al.* (1985) *EMBO J.* 4:761) and the enhancer/promoters derived from the long terminal repeat (LTR) of the Rous Sarcoma Virus (Gorman *et al.* (1982b) *Proc. Natl. Acad. Sci.* 79:6777), from human cytomegalovirus (Boshart *et al.* (1985) *Cell* 41:521) as well as the mouse μ enhancer (Gillies, *Cell* 33:717–728, 1983). Additionally, some enhancers are regulatable and become active only in the presence of an inducer, such as a hormone or metal ion (Sassone-Corsi and Borelli (1986) *Trends Genet.* 2:215; Maniatis *et al.* (1987) *Science* 236:1237).

In addition, the transcription unit can also be comprised of a termination sequence and a polyadenylation signal which are operably linked to the GBS toxin receptor coding sequence. Polyadenylation signals include, but are not limited to, the early or late polyadenylation signals from SV40 (Kaufman and Sharp), the polyadenylation signal from the Adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto *et al., Nuc. Acids Res.* 9:3719–3730, 1981).

Sequences that cause amplification of the gene may also be desirable, as are sequences which encode selectable markers. Selectable markers for mammalian cells are known in the art, and include, for example, thymidine kinase, dihydrofolate reductase (together with methotrexate as a DHFR amplifier), aminoglycoside phosphotransferase, hygromycin B phosphotransferase, asparagine synthetase, adenosine deaminase, and antibiotic resistant genes such as neomycin.

A GBS toxin receptor, or fragment thereof, can be expressed on the surface of a cell, or can be expressed in soluble or secreted form. Expression on the surface of the cell can be achieved, for example, by including a secretory leader operably linked to a nucleic acid sequence

encoding the desired receptor fragment and at least one transmembrane domain. The secretory leader can be that encoded by the GBS toxin receptor gene, or can be a heterologous leader sequence commonly used in the art, such as, for example, the leader sequence of *Schizosaccharomyces pombe* pho1$^+$ acid phosphatase (Braspenning *et al., Biochem Biophys Res. Commun.* (1998) 245:166-71), the leader sequence of human interleukin-2 (IL-2) gene (Sasada *et al., Cell Struct Funct* (1988) 13:129-141). Expression in soluble or secreted form can be achieved, for example, by excluding from the gene construct nucleic acid sequences encoding a transmembrane domain. In some instances, solubility and/or secretion are achieved by the use of a fusion partner, such as, for example, chloramphenicol acetyltransferase (CAT), β-galactosidase, and other genes readily expressed in the selected host cell.

The vector that encodes GBS toxin receptor can be used for transformation of a suitable mammalian host cell. Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus and transducing a host cell with the virus or by transfection procedures known in the art, as exemplified by U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455. The transformation procedure used depends upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including, but not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), N1E-115 (Liles *et al., J. Biol. Chem.* 261:5307–5313, 1986), PC 12 human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines, such as insect derived cell lines IF9 and IF21. Cell lines of particular preference are those expressing recombinant GBS toxin receptor constructs constitutively, lines which subsequently develop characteristics of a transformed cell, and lines that more preferably express GBS toxin receptor or fragments on the cell surface. Particularly preferred are ECV cells (a bladder carcinoma cell line originally referred to in the scientific literature as an endothelial cell line), human umbilical vein endothelial cells (HUVEC), bovine, sheep, and human adrenal medulla endothelial cells.

Recombinant GBS toxin receptor or fragments thereof can be produced by culturing host cells expressing the receptor or fragment in a suitable culture medium and under appropriate cell culture conditions. Culture media and conditions are variable depending on the requirements of a particular host cell line and are well known in the art. Typically, cells are cultured at 37°C in a cell culture incubator with a fixed amount of CO_2, usually in the range of 5-10%.

IDENTIFICATION OF OTHER GBS TOXIN RECEPTORS

In addition to the preferred GBS toxin receptors HP59 and SP55, other naturally occurring GBS toxin receptors can be used in methods, compositions and vaccines of the present invention. Nucleic acids encoding such receptors can be isolated from various tissue sources and cell cultures from different species that produce such a receptor by the methods described herein, such as, for example, cells from tumor endothelium, synovial tissue in rheumatoid arthritis, or hypoxic tissue deprived of or restricted from blood flow, such as in reperfusion injury or wounded tissue. Such polynucleotides can be isolated by hybridization using probes or by polymerase chain reaction using oligonucleotides, as well as by implementing other molecular biology techniques known in the art. Such probes and oligonucleotides typically comprise various regions of the sequence of SEQ ID NO:1 or 3, or encode various regions of the sequence of SEQ ID NO:2 or 4. Alternatively, additional target proteins for CM101 may be expression cloned. This method is described in WO 00/05375. Alternatively, subtractive hybridization between similar tissues that do and do not express the GBS toxin receptor may be used to isolate additional GBS toxin receptors. Examples of such tissues are wounded tissue and corresponding non-wounded tissue; tumor tissue and a sample of the same tissue that is free of histopathological abnormality; and lung tissue of appropriate mammals during expression of the GBS toxin receptor and shortly after expression stops. Upon discovery of an additional receptor, the probes may comprise various regions of the newly discovered receptor.

Polynucleotides useful for cloning genes encoding GBS toxin receptors of various organisms can be determined by comparing the amino acid sequences of homologous proteins. (see Table 5 which compares amino acids 41-536 of HP59 with amino acids 1-495 of SP55). For example, conserved regions can be targeted for the synthesis of oligonucleotides or degenerate oligonucleotides to be used as probes for hybridization or nucleic acid amplification, techniques discussed further below. Stringency can be varied to achieve selective hybridization conditions whereby nucleic acid sequences having less than 95% identity with respect to each other will

hybridize. These conditions are known in the art and discussed herein. Generally, the nucleic acid sequence identity between HP59 or SP55 and a nucleic acid sequence of interest will be at least about 80%, and more typically with preferably increasing identities of at least about 85% and 90%.

Polynucleotides can be used as probes under high stringency wash conditions and with corresponding hybridization conditions, as known in the art. Small polynucleotides, for example, polynucleotides 200 bases or fewer in length, are often referred to in the art as oligonucleotides. Techniques for using polynucleotides as probes to detect the same or related nucleic acid sequences is well known in the art. See, for example, Sambrook *et al*, especially Chapter 11. Usually, probes can be made from polynucleotides that are 10 to 200 bases in length. Preferably probes are made from polynucleotides 10 to 60 nucleotides in length and most preferably 12 to 40 bases in length. Specific probes can be designed based on results obtained using nucleic acid homology computer programs such as FASTA, which uses the method of Pearson and Lipman (*Proc. Natl. Acad. Sci. USA* 85:2444-2448 (1988)) and shows the degree of identity between compared sequences. The size of the probe is dependent upon the region of the gene to which it will be hybridized. The size of the probe increases as the degree of homology to undesirable nucleic acid sequences increases. A probe 10-50 nucleotides in length can be used, preferably more than 50 nucleotides, even more preferably more than 100 nucleotides, and most preferably a probe made from the entire coding region of a GBS toxin receptor will be used. To decrease the number of false positives, preferably two probes are used to identify clones that bind to both probes under hybridization and wash conditions. Oligonucleotides can be synthesized on an Applied BioSystems oligonucleotide synthesizer according to specifications provided by the manufacturer.

Typically, hybridization and washing conditions are performed at according to conventional hybridization procedures. Typical hybridization conditions for screening plaque lifts (Benton and Davis (1978) *Science* 196: 180) can be: 50% formamide, 5 x SSC (sodium chloride, sodium citrate) or SSPE (sodium chloride, sodium phosphate, EDTA), 1-5 x Denhardt's solution, 0.1-1% SDS, 100-200 μg sheared heterologous DNA or tRNA, 0-10% dextran sulfate, 1 x 10^5 to 1 x 10^7 cpm/ml of denatured probe with a specific activity of about 1 x 10^8 cpm/μg, and incubation at 42°C for about 6-36 hours. Prehybridization conditions are essentially identical except that probe is not included and incubation time is typically reduced. Washing conditions are typically 1-3 x SSC, 0.1-1% SDS, 42-70°C with change of wash solution at about 5-30 minutes. For high stringency hybridization conditions, various parameters can be altered to

increase the stringency of hybridization, such as by increasing the temperature of incubation with the labeled probe. Preferably, for greater flexibility in experimental design, the probe can be hybridized at a lower temperature, such as, for example, room temperature and the stringency can then be modified by altering the salt concentration and temperature of the wash solutions. For high stringency a wash temperature of greater than or equal to 42°C can be used, such as, for example, 68°C, in a wash buffer having a salt concentration less than 3X SSC, such as, for example, 0.1X SSC. In some cases, TMACL can also be used, particularly for polynucleotides rich in G-C base pairs in order to decrease non-specific binding. A lower stringency wash can be used to hybridize polynucleotides with lower identities or polynucleotides that are less than 60 base pairs in length. For a low stringency wash, temperatures of less than or equal to 42° can be used in a wash buffer having a salt concentration of greater than or equal to 2X SSC.

Table 5 -- Alignment of Human and Sheep GBS Toxin Receptor Amino Acid Sequences

```
SP55   MKSPVSDLAPSDGEEGSDRTPLLQRAPRAEPAPVCCSARYNLAFLSFFGF     50
       | ||| ||| |||| |||||| ||||| |||||||||||| | ||||
HP59   MRSPVRDLARNDGEESTDRTPLLPGAPRAEAAPVCCSARYNLAILAFFGF     91

SP55   FVLYSLRVNLSVALVDMVDSNTTAKDNRTSYECAEHSAPIKVLHNQTGKK    100
       | | ||||||||||||||||||| ||||| | |||||||| |||||||
HP59   FIVYALRVNLSVALVDMVDSNTTLEDNRTSKACPEHSAPIKVHHNQTGKK    141

SP55   YRWDAETQGWILGSFFYGYIITQIPGGYVASRSGGKLLLGFGIFATAIFT    150
       | |||||||||||||||||||||||||||||| ||| |||||| || |
HP59   YQWDAETQGWILGSFFYGYIITQIPGGYVASKIGGKMLLGFGILGTAVLT    191

SP55   LFTPLAADFGVGALVALRALEGLGEGVTYPAMHAMWSSWAPPLERSKLLS    200
       |||| ||| ||| | |||||||||||| ||||||||||||||||||||
HP59   LFTPIAADLGVGPLIVLRALEGLGEGVTFPAMHAMWSSWAPPLERSKLLS    241

SP55   ISYAGAQLGTVVSLPLSGVICYYMNWTYVFYFFGIVGIIWFILWICLVSD    250
       |||||||||| |||||| |||||||||||||| || || ||| ||||
HP59   ISYAGAQLGTVISLPLSGIICYYMNWTYVFYFFGTIGIFWFLLWIWLVSD    291

SP55   TPETHKTITPYEKEYILSSLKNQLSSQKSVPWIPMLKSLPLWAIVVAHFS    300
       || || | |||||||||| |||||||||| | ||||||||||||||||
HP59   TPQKHKRISHYEKEYILSSLRNQLSSQKSVPWVPILKSLPLWAIVVAHFS    341

SP55   YNWTFYTLLTLLPTYMKEVLRFNIQENGFLSAVPYLGCWLCMILSGQAAD    350
       |||||||||||||||||| |||| ||||||| |||| ||||||||||||
HP59   YNWTFYTLLTLLPTYMKEILRFNVQENGFLSSLPYLGSWLCMILSGQAAD    391

SP55   NLRARWNFSTLWVRRVFSLIGMIGPAIFLVAAGFIGCDYSLAVAFLTIST    400
       |||| |||||| ||| |||||||||| ||||||||||||||||||||||
HP59   NLRAKWNFSTLCVRRIFSLIGMIGPAVFLVAAGFIGCDYSLAVAFLTIST    441
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SP55  TLGGFCSSGFSINHLDIAPSYAGILLGITNTFATIPGMIGPIIARSLTPE   450
      ||||||||||||||||||||||||||||||||||||||| || || ||||
HP59  TLGGFCSSGFSINHLDIAPSYAGILLGITNTFATIPGMVGPVIAKSLTPD   491

SP55  NTIGEWQTVFCIAAAINVFGAIFFTLFAKGEVQNWAISDHQGHRN       495
      || ||||||| ||||||||||||||||||||||||  || |||
HP59  NTVGEWQTVFYIAAAINVFGAIFFTLFAKGEVQNWALNDHHGHRH       536
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VACCINE PREPARATION

A preferred embodiment of the present invention is a conjugate vaccine in which the GBS toxin receptor or fragment thereof is covalently linked to a "carrier" protein or polypeptide. The linkage serves to increase the antigenicity of the GBS toxin receptor polypeptide. Methods for forming conjugate vaccines from an antigenic molecule and a "carrier" protein or polypeptide are known in the art (Jacob, C. O, *et al., Eur. J. Immunol.* 16:1057-1062 (1986); Parker, J. M. R. et al., In: MODERN APPROACHES TO VACCINES, Chanock, R. M. *et al.,* eds, pp. 133-138, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1983); Zurawski, V. R, *et al., J. Immunol.* 121:122-129 (1978); Klipstein, F. A, *et al., Infect. Immun.*37:550-557 (1982); Bessler, W. G, *Immunobiol.* 170:239-244 (1985); Posnett, D. N, *et al., J. Biol. Chem.* 263:1719-1725 (1988); Ghose, A. C, *et al., Molec. Immunol.* 25:223-230 (1988)). A prototype model for conjugate vaccines was developed against *Hemophilus influenzae* (Anderson, P, *Infec. and Immun.* 39:223-238 (1983); Chu, C, *et al., Infect. Immun.* 40:245-256 (1983); Lepow, M, *Pediat. Infect. Dis. J.* 6:804-807 (1987)), and this model may be employed in constructing the novel vaccines of the present invention. Additional methods for producing such a conjugate vaccine are disclosed by Anderson, P. W, *et al.*, European Patent Publication 245,045; Anderson, P. W, *et al.,* U.S. Pat. Nos. 4,673,574 and 4,761,283; Frank, R. et al., U.S. Pat. No. 4,789,735; European Patent Publication No. 206,852; Gordon, L. K, U.S. Pat. No. 4,619,828; and Beachey, E. H, U.S. Pat. No. 4,284,537. Useful carriers include keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA), ovalbumin, human serum albumin, human gamma globulin, chicken immunoglobulin G, bovine gamma globulin and tetanus toxoid. Alternatively, the GBS toxin polypeptide may be conjugated or linked to immunogenic polysaccharides such as group A *Streptococci* polysaccharide, C-polysaccharide from group B *Streptococci*, or the capsular polysaccharide of *Streptococci pnuemoniae*.

Another embodiment of the present invention is a whole cell vaccine in which the transfected or normal cell expressing a GBS toxin receptor on its membrane may be alive or fixed and killed.

As would be understood by one of ordinary skill in the art, when the vaccine of the present invention is provided to an individual, it may be in a composition which may contain salts, buffers, adjuvants, or other substances which are desirable for improving the efficacy of the composition. Normally, the adjuvant and the composition are mixed prior to presentation to the immune system, or presented separately, but into the same site of the mammal being immunized. Alum is a registered adjuvant for human use. Other adjuvants are being developed for human use and it is anticipated that these other adjuvants would be suitable for use in preparing compositions for human vaccination in accordance with this invention. Suitable adjuvants for the vaccination of animals include but are not limited to oil emulsions such a Freund's complete or incomplete adjuvant (not suitable for livestock use), Marcol 52: Montanide 888 (Marcol is a Trademark of Exxon. Montanide is a Trademark of SEPPIC, Paris), squalane or squalene, Adjuvant 65 (containing peanut oil, mannide monooleate and aluminium monostearate), mineral gels such as aluminium hydroxide, aluminium phosphate, calcium phosphate and alum, surfactants such a hexadecylamine, octadecylamine, lysolecithin, dimethyldioctadecylammonium bromide, N,N-dioctadecyl-N',N'-bis(2-hydroxyethyl) propanediamine, methoxyhexadecylglycerol and pluronic polyols, polyanions such as pyran, dextran sulfate, polyacrylic acid and carbopol, peptides and amino acids such as muramyl dipeptide, dimethylglycine, tuftsin and trehalose dimycolate.

The polypeptides of the present invention can also be administered following incorporation into liposomes or other micro-carriers.

PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions of the invention preferably include a pharmaceutically acceptable carrier that may contain a variety of components that provide a variety of functions, including regulation of drug concentration, regulation of solubility, chemical stabilization, regulation of viscosity, absorption enhancement, regulation of pH, and the like. For example, in water soluble formulations the pharmaceutical composition preferably includes a buffer such as a phosphate buffer, or other organic acid salt, preferably at a pH of between about 7 and 8. Other components may include antioxidants, such as ascorbic acid, hydrophilic polymers, such as, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, dextrins, chelating agents, such as EDTA, and like components well known to those in the pharmaceutical sciences, e.g. REMINGTON'S PHARMACEUTICAL SCIENCE, 19th edition (Mack Publishing Company, Easton, PA).

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble, alkali metal or alkaline-earth metal salts previously enumerated. Such aqueous solutions should be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. Solutions of the GBS toxin receptor polypeptide as a free base or a pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of a dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the GBS toxin receptor polypeptide in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those

enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yield a powder of the active ingredient plus any additional desired ingredient from the previously sterile-filtered solution thereof.

Intranasal formulations may include vehicles that neither cause irritation to the nasal mucosa nor significantly disturb ciliary function. Diluents such as water, aqueous saline or other known substances can be employed with the subject invention. The nasal formulations may also contain preservatives such as, but not limited to, chlorobutanol and benzalkonium chloride. A surfactant may be present to enhance absorption of the subject proteins by the nasal mucosa.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be presented dry in tablet form or a product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservative.

ADMINISTRATION

ROUTE

The polypeptides, compositions and vaccines of the present invention can be administered orally, parenterally by injection, rapid infusion, nasopharyngeal absorption (intranasopharangeally), dermoabsorption, or rectally. They may alternatively be administered intramuscularly, or intravenously. Compositions for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Carriers or occlusive dressings can be used to increase skin permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable forms for suspending liposomes include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water. Besides the inert diluents, such compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, and the like.

DOSAGE AND FREQUENCY OF ADMINISTRATION

The amount of GBS toxin receptor polypeptide to be combined with carrier, diluent, excipient and/or adjuvant to produce a single pharmaceutical composition or vaccine dosage form will vary depending upon the pathoangiogenic condition being vaccinated against, the mammal's propensity for developing such condition or the severity of such condition, the mammal to be treated and the particular time and route of administration. It will be understood, also, that the specific dose level for any particular mammal will depend upon a variety of factors including the age, body, weight, general health, sex, and diet of such mammal. Effective dosages can be readily established by one of ordinary skill in the art through routine trials establishing dose-response curves.

Many different techniques exist for the timing of the immunizations when a multiple administration regimen is utilized. It is possible to use the compositions of the invention more than once to increase the level, diversity and stability of the immune response in the immunized animal. Multiple doses may be required to maintain a state of immunity to GBS toxin receptor. If so, multiple immunizations will be given at intervals appropriate to maintain the desired immune response.

MONITORING IMMUNE RESPONSE

It is desirable to characterize the immune response of a mammal that has received a vaccine according to the method of the present invention. Such characterization is preferably made in light of the mammal's immune response to the GBS toxin receptor and to various other standards prior to the initial administration of the receptor. Subsequent testing is performed within a reasonable period, preferably at least six weeks, after administration of the GBS toxin receptor. Such testing may be performed again at regular intervals thereafter or on an as-needed basis, depending on the mammal's condition. For instance, at the desired timepoint, a blood sample is harvested from the mammal and preserved in an appropriate manner until testing can be carried out. Preservation methods of the blood samples include separation of blood sera from other blood components, cooling or freezing, and preservation with various buffering or anti-coagulatory agents. Testing may also be performed on urine, stool, and tissue from lung, lymph nodes, spleen, bond marrow, ulcers, skin lesions and exudate and other tissues affected by the pathoangiogenic condition being tested.

The presence of antibodies in the serum (i.e. a humoral immune response to the GBS toxin receptor) may be determined by ELISA, RAST, EIA, hemagglutination inhibition,

other radioimmunoassay techniques, and latex agglutination methods and by general serological assays including white blood cell counts, measurement of total and differentiated immunoglobulin levels, including IgM, total IgG, IgG_1, IgG_2, IgG_3 and IgG_4, or other methods known to one of skill in the art. One possible method for performing an ELISA determination involves plating the GBS toxin receptor of interest onto ELISA plates. After unbound antigen is washed off the plates, excess protein reactive sites on the plates are blocked with a blocking buffer. Following removal of the blocking buffer, a dilution series of sera in PBS is added into wells of the blocked ELISA plates and incubated for one hour at 37°C. After removal of the dilution series, the plates are washed and a conjugated antibody solution in PBS (antibody is against the vaccinated species) is added to the wells of the ELISA plate, which is then incubated for one hour at 37°C. After removal of the conjugated antibody solution, the plates are washed and the appropriate chromogenic substrate is added to the wells to allow for color development. After a 30-minute incubation, color development is stopped and the absorbance readings of the wells are read on a spectrophotometer. The absorbance readings for each group at each dilution are averaged and plotted versus the reciprocal dilution. Positive and negative controls are an important part of this determination as is a comparison with the pre-immunization (baseline) testing. If antibodies can be detected at a dilution of about 1:200 or more, then the mammal has a positive immune response.

Determination of a cellular immune response may be made by methods known to those of skill in the art, including those discussed herein. The presence of T cells that recognize the GBS toxin receptor can be tested by administering a sample of the GBS toxin receptor subcutaneously and examining the skin of the mammal (preferably human) 72 hours later to see if the skin at the site of administration is raised by about 1mm or more. The size of such wheals are typically measured and can be correlated to the degree of immune response. Such a response is a positive immune response. Alternatively, a cellular immune response can be determined by such methods as measuring C-reactive protein serum levels, complement levels, including normal complement and C-3 detection, erythrocyte sedimentation rate, haptoglobin serum levels, immunoprotein levels and other protein serum levels.

A positive immune response means that the pathoangiogenic condition is prevented or attenuated. Prevention and attenuation can be demonstrated by methods known in the art, including but not limited to those discussed herein.

One method of demonstrating prevention is to administer the vaccine to or practice the method upon a group of individuals from a population that is susceptible to the

pathoangiogenic condition of interest and compare the incidence of the condition in such group with the incidence of the condition in the rest of the population that did not receive the vaccine or method. For example, humans who smoke are susceptible to lung cancer. A group from a test population of statistically matched smokers who do not have lung cancer can be given a vaccine or method of the present invention while the remainder of the test population will not receive any treatment. Both groups are monitored for lung cancer. If no members of the group that received the vaccine or method have developed lung cancer by a time when a statistically significant number of the remainder of the test population have developed the disease, then the vaccine or method can be concluded to prevent lung cancer. If cases of lung cancer develop in the treated group but do so at a statistically significant lower rate than that of the remainder of the population, the vaccine or method can be concluded to decrease the incidence of lung cancer. One of skill in the art can demonstrate prevention of other pathoangiogenic conditions by similar methods known in the art including testing of populations that are susceptible to the particular disease on account of genetic and/or environmental factors.

Support for additional aspects of the present invention and methods for making and using the invention are published in WO 00/05375.

EXAMPLES

Example 1. Immunization with a mixture of three fragments from human GBS toxin receptor retards tumor growth.

Peptides Hab1, Hab2 and Hab3, which are shown in Table 3, are fragments from amino terminus of HP59 that were selected as immunogens based on hydrophilicity. They were synthesized *in vitro* (Sigma-Genosis, The Woodlands, Texas) and conjugated to keyhole limpet hemocyanin (KLH), a glycoprotein which served as an adjuvant. Experimental C57 mice (n=8, four males and four females) were immunized by subcutaneous injection of 100 micrograms of a mixture of the three peptide conjugates in complete Freund's adjuvant (CFA). Two weeks, four weeks and six weeks later, each of these mice received a subcutaneous injection of 100 micrograms of this mixture in incomplete Freund's adjuvant (IFA). A final injection of 100 micrograms of this mixture in IFA was given intradermally at eight weeks. Control C57 mice (n=8) were immunized at the same times in the same manner with only KLH and Freund's adjuvant.

Experimental mice were bled from the tail vein 6 weeks after the initial immunization and every four weeks thereafter and the level of antibodies formed to the HP59 derived peptides were established by ELISA. When a positive antibody titer was obtained from all experimental mice, both control and experimental mice were challenged with tumor cells as follows: 50,000 mouse melanoma B1-6 cells or Lewis lung tumor cells were suspended in 0.6% agar and injected subdermally. The volume of the tumors was measured 6, 8, 10, 12 and 14 days after the tumor cell injections. As shown in Table 6, the melanoma tumors of immunized mice were 45% smaller than those of their control counterparts and the Lewis lung tumors of immunized mice were 38% smaller than those of their control counterparts. The results of both experiments were statistically significant. For the melanoma experiments, the paired t test for treated versus control was t=2.3898 with five degrees of freedom and the one tailed p=0.0312, which is considered significant. For the Lewis lung experiments, the paired t test for treated versus control was t=2.9899 with five degrees of freedom and the one tailed p=0.0152, which is considered significant.

TABLE 6. Tumor progression (volume = # x mm^3)

Tumor Type	Day 6	Day 8	Day 10	Day 12	Day 14
Melanoma (n=4)	15.6	83.3	131.3	350.1	429.8
Control (n=4)	20.4	118.2	174.5	518.6	783.5
Lewis Lung (n=4)		36.9	70.8	144.8	194.6
Control (n=4)		68.8	119.4	178.8	315.1

Example 2. Treatment of immunized mammals with CM101

Mice immunized and challenged with tumor cells as described in Example 1 may additionally receive weekly intravenous infusions of 60μg/kg of the GBS toxin CM101 (CarboMed, Inc., Brentwood, TN) or mock injections. Tumor progression is compared in the CM101-treated and control mice and the degree of tumor growth retardation or elimination is calculated using standard statistical methods. Additional experiments at different dose levels are conducted to determine a dose-response relationship.

Example 3. Treatment of immunized mammals with immunocompatible antibodies

Mice immunized and challenged with tumor cells as described in Example 1 may additionally receive weekly injections of 100μg of a mixture of mouse monoclonal antibodies specific for HP59 or mock injections. Such antibodies are obtained by immunizing mice with

100mg of the synthetic peptides shown in Table 3 in accordance with the methods taught in Harlow *et al.*, ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Press, pp.139-240 (1989). Tumor progression is compared in the antibody-treated and control mice and the degree of tumor growth retardation or elimination is calculated using standard statistical methods. Additional experiments at different dose levels are conducted to determine a dose-response relationship.

Example 4. Treatment of immunized mammals with autologous T cells

T cells may be removed from mice immunized and challenged with tumor cells as described in Example 1 and either incubated with a mixture of the Hab1, Hab2 and Hab3 peptides or mock incubated for 72 hours. The T cells are returned to each donor mouse by intravenous injection. Tumor progression is compared in the peptide-incubated and control mice and the degree of tumor growth retardation or elimination is calculated using standard statistical methods. Additional experiments at different dose levels are conducted to determine a dose-response relationship.

Example 5. Immunization with a mixture five fragments from human and sheep GBS toxin receptors retards tumor growth

Two groups of male and female C57 mice and equal size controls were immunized with a mixture of five peptides shown in Tables 3 and 4, p56a, p55a, p57a, Hab1, and Hab2. These peptides were derived from the homologous proteins HP59 and SP55 (87%), conjugated with keyhole limpet hemocyanin (KLH) (Sigma Genosys, TX) and emulsified in complete Freund's Adjuvant (CFA), by intradermal injection in three places at the base of the tail.

The first immunization was followed two weeks and four weeks later with repeat intradermal injections of antigen KLH conjugate and incomplete Freund's Adjuvant (IFA) for the experimental group. IFA alone was given to control animals. Animals were bled after 5 weeks and shown to have antibody titer of 1:200 with optical density (O.D.) of >2.0. to one extracellular peptide based on a seven transmembrane domain (7TMD) configuration.

Lewis Lung cell suspension ($5x10^4$ cells) in 3% agar was implanted subcutaneously in seven immunized male and five immunized females. Four male and four female CFA and IFA immunized mice served as controls. The mice were observed until the

control tumors began to ulcerate at which time mice were sacrificed and tissues, including tumors, were collected.

The growth curve for the Lewis Lung tumors in C57 mice are shown in Fig. 1. The y-axis represents tumor volume and the x-axis represents the day the tumor volume was measured. Male controls are denoted by blackened diamonds, female controls are denoted by blackened circles; male immunized are denoted by clear circles and female immunized are denoted by clear diamonds. The raw data of tumor volumes from different days were recorded. A paired t-test using tumor volumes at the five last measurements shows a significant difference ($p=0.025$) in the average tumor volumes for the non-immunized male and female with the average for the immunized groups. The overall tumor burden in the immunized mice was only 38.3% of the control.

Example 6. Retardation of melanomas in female mammals

Five each of HP59/CFA and CFA immunized, female C57 mice were inoculated intravenously with 1,000 melanoma cells. Time to death was the endpoint. Mice were to be sacrificed when respiratory distress was obvious.

The five female controls died on days 46, 52, 54, 62 and 100. The autopsy of the diseased control mice showed lungs to be infiltrated by numerous metastasis. One immunized female died early with no sign of tumors. The remaining four immunized mice were all alive at day 140 with no signs of disease, at which time two of them were inoculated with an additional 1,000 melanoma cells (denoted by an arrow in Fig. 2). The remaining four immunized mice continued to show no signs of disease on day 305. Fig. 2 shows survival curves for the female mice challenged intravenously with 1000 melanoma cells. The y-axis represents percentage of survivors and the x-axis represents the number of days of survival. The blackened circles denote female controls and the blackened squares denote female immunized mammals.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patents or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method of preventing a pathoangiogenic condition in a mammal comprising:

administering to said mammal an amount of one or more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain an immune response to at least one of the GBS toxin receptors.

2. A method of attenuating a pathoangiogenic condition in a mammal comprising:

administering to said mammal an amount of one or more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain an immune response to at least one of the GBS toxin receptors.

3. The method of claim 1 or 2, wherein the pathoangiogenic condition is selected from the group consisting of cancer, scarring during wound healing, gliosis during repair of nerve injury, chronic wounds, keloids, reperfusion injury, rheumatoid arthritis, atherosclerosis, osteoarthritis and psoriasis.

4. The method of claim 1 or 2, wherein at least one GBS toxin receptor has substantial identity to SEQ ID NO:2.

5. The method of claim 4, wherein at least one GBS toxin receptor is identical to SEQ ID NO:2, or is SEQ ID NO:2 with at least one conservative amino acid substitution.

6. The method of claim 1 or 2, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:2.

7. The method of claim 6, wherein at least one immunogenic fragment has substantial identity to Hab1, Hab2, Hab3 or Hab4.

8. The method of claim 1 or 2, wherein at least one GBS toxin receptor has substantial identity to SEQ ID NO:4.

9. The method of claim 8, wherein at least one other GBS toxin receptor has substantial identity to SEQ ID NO:2.

10. The method of claim 8, wherein at least one GBS toxin receptor is identical to SEQ ID NO:4, or is SEQ ID NO:4 with at least one conservative amino acid substitution.

11. The method of claim 1 or 2, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:4.

12. The method of claim 11, wherein each of two or more immunogenic fragments has substantial identity to a portion of SEQ ID NO:4.

13. The method of claim 11, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:2.

14. The method of claim 12, wherein at least one immunogenic fragment has substantial identity to p55a, p56a or p57a.

15. The method of claim 1 or 2, wherein the normal tissue of the mammal does not contain the GBS toxin receptor.

16. The method of claim 1 or 2, wherein the administering is via a method selected from the group consisting of oral ingestion, nasal inhalation, subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection or rectal application.

17. The method of claim 2, wherein the mammal does not have the pathoangiogenic condition at the time of the administering step.

18. The method of claim 2, wherein the mammal has a pathoangiogenic condition at the time of the administering step.

19. The method of claim 2, further comprising administering to said mammal an amount of GBS toxin sufficient to induce a response.

20. The method of claim 19, wherein the amount of GBS toxin is at least about 5 μg/kg.

21. The method of claim 20, wherein the amount of GBS toxin is at least about 15 μg/kg.

22. The method of claim 21, wherein the amount of GBS toxin is at least about 20 μg/kg.

23. The method of claim 2, further comprising administering an effective amount of one or more immunocompatible antibodies that bind to a GBS toxin receptor.

24. A method of preventing or attenuating a pathoangiogenic condition in a mammal comprising:

administering to said mammal immunocompatible antibodies that bind to a GBS toxin receptor.

25. The method of claim 23 or 24, wherein each immunocompatible antibody is a monoclonal antibody.

26. The method of claim 23 or 24, wherein each immunocompatible antibody is obtained from a polyclonal serum.

27. The method of claim 23 or 24, wherein at least some of the immunocompatible antibodies further comprise a cytotoxic agent.

28. The method of claim 2, further comprising removing T cells from the mammal, culturing the T cells with a GBS toxin receptor, and returning the T cells to the mammal.

29. A composition comprising one or more GBS toxin receptors or immunogenic fragments thereof.

30. The composition of Claim 29 wherein the one or more GBS toxin receptors or immunogenic fragments thereof are in an amount effective for protecting against or attenuating a pathoangiogenic condition.

31. The composition of Claim 30 further comprising a pharmaceutically acceptable excipient.

32. The composition of claim 30, wherein at least one of the GBS toxin receptors or fragments thereof is isolated.

33. The composition of claim 30, further comprising an adjuvant.

34. The composition of claim 33, wherein said adjuvant is selected from the group consisting of: a water in oil composition, Freund's adjuvant, QS21, IL-12 and interferon gamma.

35. The composition of claim 32, wherein one of the isolated GBS toxin receptors or fragments thereof is conjugated or linked to a protein carrier.

36. The composition of claim 35, wherein the protein carrier is a molecule selected from the group consisting of keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA), ovalbumin, human serum albumin, human gamma globulin, chicken immunoglobulin G, bovine gamma globulin and tetanus toxoid.

37. The composition of claim 30, wherein at least one of the GBS toxin receptors or fragments thereof is glycosylated.

38. The composition of claim 30, wherein at least one isolated GBS toxin receptor or fragment thereof is recombinant or synthetic.

39. The composition of claim 30, wherein the pathoangiogenic condition is selected from the group consisting of cancer, scarring during wound healing, gliosis during repair of nerve injury, chronic wounds, keloids, reperfusion injury, rheumatoid arthritis, atherosclerosis, osteoarthritis and psoriasis.

40. The composition of claim 30, wherein at least one GBS toxin receptor has substantial identity to SEQ ID NO:2.

41. The composition of claim 40, wherein at least one GBS toxin receptor is identical to SEQ ID NO:2, or is SEQ ID NO:2 with at least one conservative amino acid substitution.

42. The composition of claim 40, wherein at least one other GBS toxin receptor has substantial identity to SEQ ID NO:4.

43. The composition of claim 30, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:2.

44. The composition of claim 43, wherein at least one immunogenic fragment has substantial identity to Hab1, Hab2, Hab3 or Hab4.

45. The composition of claim 30, wherein at least one GBS toxin receptor has substantial identity to SEQ ID NO:4.

46. The composition of claim 45, wherein at least one GBS toxin receptor is identical to SEQ ID NO:4, or is SEQ ID NO:4 with at least one conservative amino acid substitution.

47. The composition of claim 30, wherein at least one immunogenic fragment has substantial identity to a portion of SEQ ID NO:4.

48. The composition of claim 47, wherein at least one immunogenic fragment has substantial identity to p55a, p56a or p57a.

49. The composition of claim 30, further comprising an effective amount of one or more immunocompatible antibodies that bind to a GBS toxin receptor.

50. A composition comprising:
antibodies that bind to a GBS toxin receptor.

51. The composition of claim 49 or 50, wherein each antibody is a monoclonal antibody.

52. The composition of claim 49 or 50, wherein each antibody is obtained from a polyclonal serum.

53. The composition of claim 49 or 50, wherein at least one of the antibodies further comprises a cytotoxic agent.

54. The composition of claim 30, further comprising T cells from the mammal that have been cultured with a GBS toxin receptor.

55. A method of producing a composition for treatment and/or prevention of pathoangiogenic conditions comprising:

providing at least one GBS toxin receptor or immunogenic fragment thereof; and

formulating the receptor or fragment in a pharmaceutically acceptable excipient.

56. The method of claim 55 further comprising providing an adjuvant.

57. A method of eliciting an immune response in an animal comprising:

administering to said mammal an amount of one or more GBS toxin receptors or immunogenic fragments thereof effective to induce or maintain an immune response to at least one of the GBS toxin receptors.

58. The method of claim 57 wherein the one or more immunogenic fragment is chosen from the group comprising residues 14-19 of SEQ. ID NO:4, residues 75-80 of SEQ. ID NO:4, residues 25-30 of SEQ. ID NO:4, Hab1, Hab2, Hab3, Hab4, p56a, p55a, and p57a.

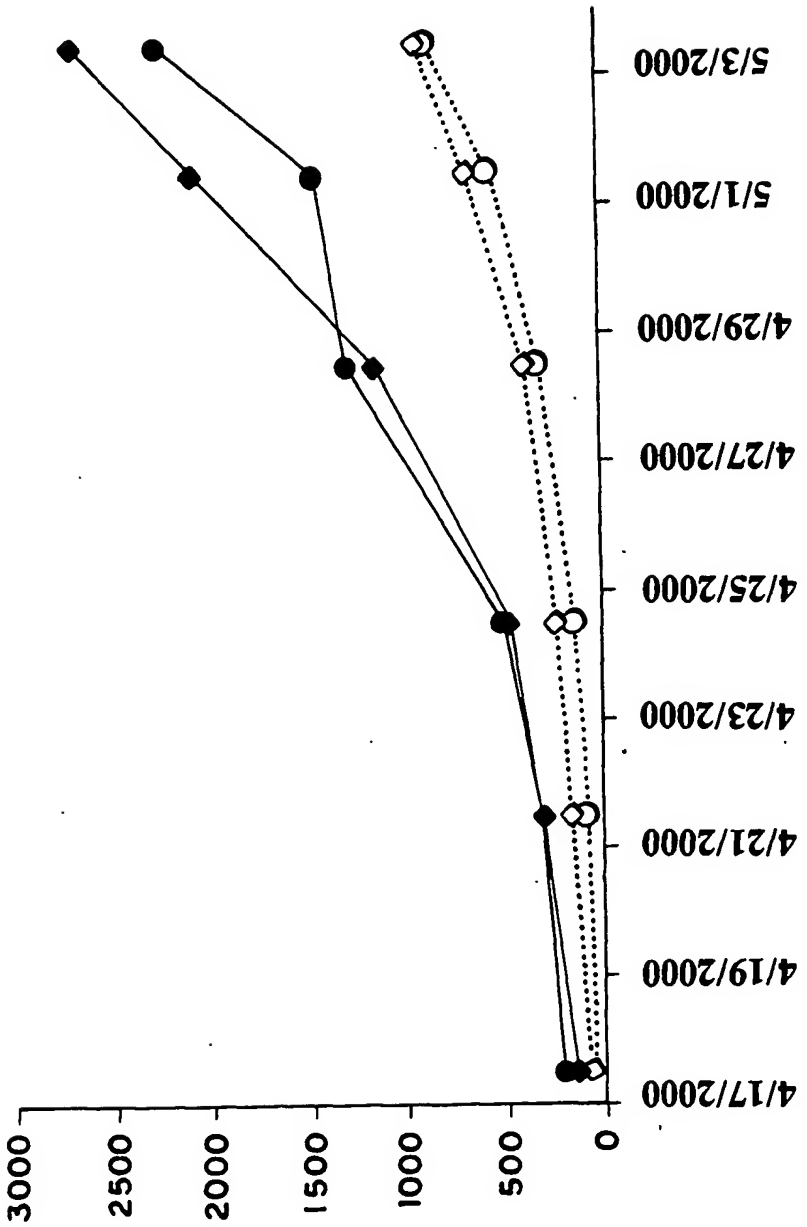
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Fig. 1

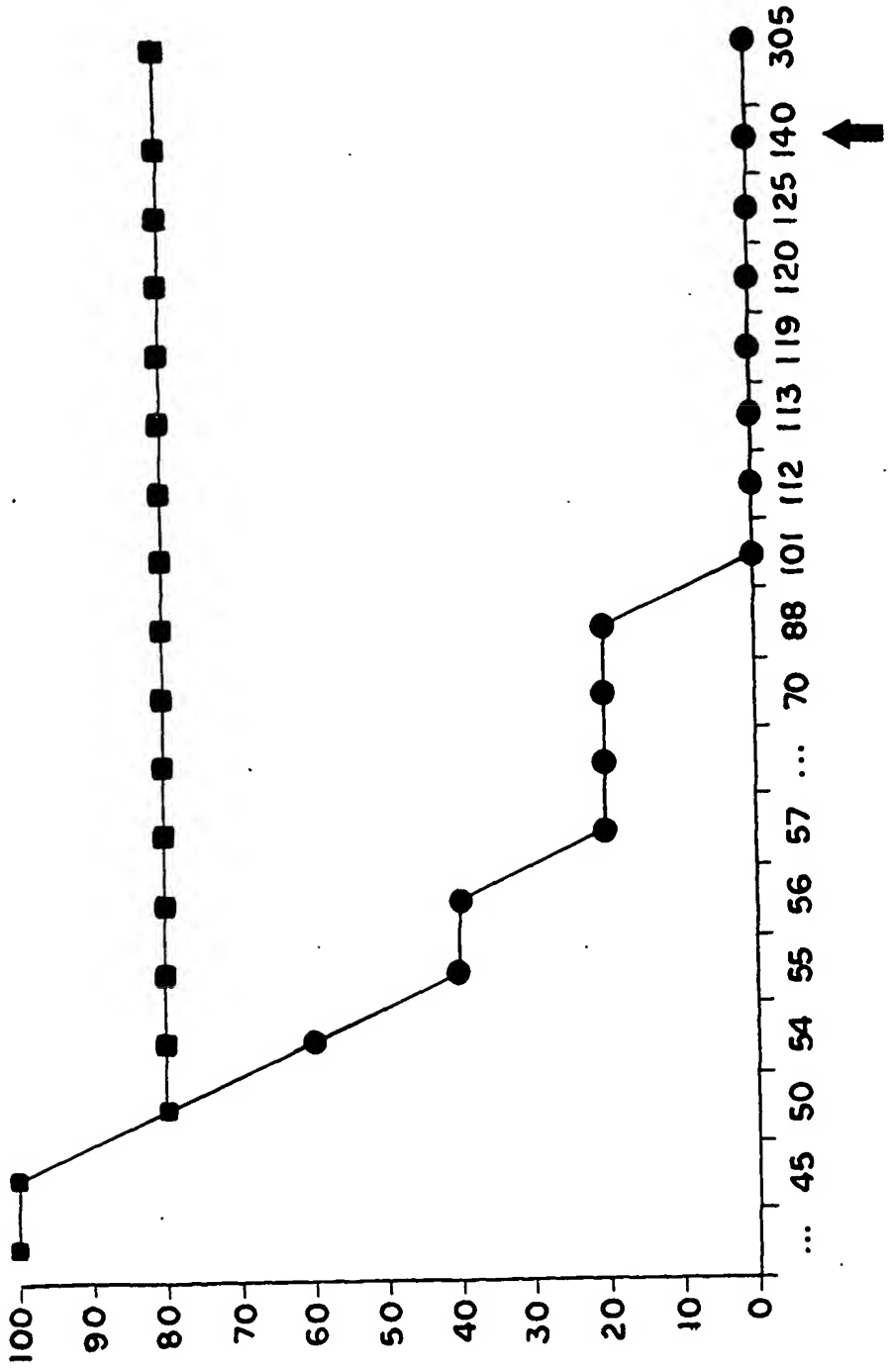
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Fig. 2

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Ala Lys Trp Asn Phe Ser Thr Leu Cys Val Arg Arg Ile Phe Ser Leu
395                 400                 405                 410

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Ile Gly Met Ile Gly Pro Ala Val Phe Leu Val Ala Ala Gly Phe Ile
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Gly Cys Asp Tyr Ser Leu Ala Val Ala Phe Leu Thr Ile Ser Thr Thr
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Leu Gly Gly Phe Cys Ser Ser Gly Phe Ser Ile Asn His Leu Asp Ile
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gct cct tcg tat gct ggt atc ctc ctg ggc atc aca aat aca ttt gcc     1684
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Leu Ala Arg Asn Asp Gly Glu Glu Ser Thr Asp Arg Thr Pro Leu Leu
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Pro Gly Ala Pro Arg Ala Glu Ala Ala Pro Val Cys Cys Ser Ala Arg
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Tyr Asn Leu Ala Ile Leu Ala Phe Phe Gly Phe Phe Ile Val Tyr Ala
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Leu Arg Val Asn Leu Ser Val Ala Leu Val Asp Met Val Asp Ser Asn
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Thr Thr Leu Glu Asp Asn Arg Thr Ser Lys Ala Cys Pro Glu His Ser
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Ala Pro Ile Lys Val His His Asn Gln Thr Gly Lys Lys Tyr Gln Trp
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Asp Ala Glu Thr Gln Gly Trp Ile Leu Gly Ser Phe Phe Tyr Gly Tyr
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Ile Ile Thr Gln Ile Pro Gly Gly Tyr Val Ala Ser Lys Ile Gly Gly
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Lys Met Leu Leu Gly Phe Gly Ile Leu Gly Thr Ala Val Leu Thr Leu
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Phe Thr Pro Ile Ala Ala Asp Leu Gly Val Gly Pro Leu Ile Val Leu
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Arg Ala Leu Glu Gly Leu Gly Glu Gly Val Thr Phe Pro Ala Met His
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Ser Ile Ser Tyr Ala Gly Ala Gln Leu Gly Thr Val Ile Ser Leu Pro
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Phe Phe Gly Thr Ile Gly Ile Phe Trp Phe Leu Leu Trp Ile Trp Leu
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Val Ser Asp Thr Pro Gln Lys His Lys Arg Ile Ser His Tyr Glu Lys
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Glu Tyr Ile Leu Ser Ser Leu Arg Asn Gln Leu Ser Ser Gln Lys Ser
305 310 315 320

Val Pro Trp Val Pro Ile Leu Lys Ser Leu Pro Leu Trp Ala Ile Val
325 330 335

Val Ala His Phe Ser Tyr Asn Trp Thr Phe Tyr Thr Leu Leu Thr Leu
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Leu Pro Thr Tyr Met Lys Glu Ile Leu Arg Phe Asn Val Gln Glu Asn
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Gly Phe Leu Ser Ser Leu Pro Tyr Leu Gly Ser Trp Leu Cys Met Ile
370 375 380

Leu Ser Gly Gln Ala Ala Asp Asn Leu Arg Ala Lys Trp Asn Phe Ser
385 390 395 400

Thr Leu Cys Val Arg Arg Ile Phe Ser Leu Ile Gly Met Ile Gly Pro
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Ala Val Ala Phe Leu Thr Ile Ser Thr Thr Leu Gly Gly Phe Cys Ser
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Trp Gln Thr Val Phe Tyr Ile Ala Ala Ala Ile Asn Val Phe Gly Ala
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Met Lys Ser Pro Val Ser Asp Leu Ala Pro
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Ser Asp Gly Glu Glu Gly Ser Asp Arg Thr Pro Leu Leu Gln Arg Ala
15 20 25

ccg cgg gcg gaa ccc gct cca gta tgc tgc tct gct cgt tac aac cta 209
Pro Arg Ala Glu Pro Ala Pro Val Cys Cys Ser Ala Arg Tyr Asn Leu
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Ala Phe Leu Ser Phe Phe Gly Phe Phe Val Leu Tyr Ser Leu Arg Val

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aat ctg agc gtt gca cta gtg gac atg gtg gat tca aac aca act gcc      305
Asn Leu Ser Val Ala Leu Val Asp Met Val Asp Ser Asn Thr Thr Ala
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aaa gat aat aga acg tcc tac gag tgt gca gag cat tct gct ccc ata      353
Lys Asp Asn Arg Thr Ser Tyr Glu Cys Ala Glu His Ser Ala Pro Ile
75                  80                  85                  90

aaa gtt ctt cac aac caa acg ggt aaa aag tac cgg tgg gat gca gaa      401
Lys Val Leu His Asn Gln Thr Gly Lys Lys Tyr Arg Trp Asp Ala Glu
                95                  100                 105

act caa gga tgg att ctc gga tct ttt ttc tat ggc tac atc atc aca      449
Thr Gln Gly Trp Ile Leu Gly Ser Phe Phe Tyr Gly Tyr Ile Ile Thr
            110                 115                 120

caa att cct gga gga tat gtt gcc agc aga agt ggg ggg aag ctg ttg      497
Gln Ile Pro Gly Gly Tyr Val Ala Ser Arg Ser Gly Gly Lys Leu Leu
        125                 130                 135

cta gga ttc ggg atc ttt gct aca gct atc ttc acc ctg ttc act ccc      545
Leu Gly Phe Gly Ile Phe Ala Thr Ala Ile Phe Thr Leu Phe Thr Pro
    140                 145                 150

ctc gct gca gat ttc gga gtc gga gcc ctt gtt gca ctc agg gca cta      593
Leu Ala Ala Asp Phe Gly Val Gly Ala Leu Val Ala Leu Arg Ala Leu
155                 160                 165                 170

gaa ggg cta gga gag ggt gtc aca tat cca gcc atg cat gcc atg tgg      641
Glu Gly Leu Gly Glu Gly Val Thr Tyr Pro Ala Met His Ala Met Trp
                175                 180                 185

tct tca tgg gct ccc cct ctt gaa aga agc aag ctt ctg agt att tca      689
Ser Ser Trp Ala Pro Pro Leu Glu Arg Ser Lys Leu Leu Ser Ile Ser
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tat gca gga gca caa ctt ggg aca gta gtt tct ctt cct ctt tct gga      737
Tyr Ala Gly Ala Gln Leu Gly Thr Val Val Ser Leu Pro Leu Ser Gly
        205                 210                 215

gta att tgc tac tat atg aat tgg act tat gtc ttc tat ttc ttt ggc      785
Val Ile Cys Tyr Tyr Met Asn Trp Thr Tyr Val Phe Tyr Phe Phe Gly
    220                 225                 230

att gtt gga atc atc tgg ttt att tta tgg atc tgc tta gtt agt gat      833
Ile Val Gly Ile Ile Trp Phe Ile Leu Trp Ile Cys Leu Val Ser Asp
235                 240                 245                 250

aca cca gaa act cac aag aca atc act ccc tat gaa aag gag tat att      881
Thr Pro Glu Thr His Lys Thr Ile Thr Pro Tyr Glu Lys Glu Tyr Ile
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ctt tca tca tta aaa aat cag ctc tct tca cag aag tca gtg ccg tgg      929
Leu Ser Ser Leu Lys Asn Gln Leu Ser Ser Gln Lys Ser Val Pro Trp
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ata cct atg ctg aaa tca ctg cca ctt tgg gct att gtc gtt gca cat      977
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Phe Ser Tyr Asn Trp Thr Phe Tyr Thr Leu Leu Thr Leu Leu Pro Thr
    300                 305                 310

tac atg aag gaa gtc cta agg ttc aat att caa gag aat ggg ttt tta     1073
Tyr Met Lys Glu Val Leu Arg Phe Asn Ile Gln Glu Asn Gly Phe Leu
315                 320                 325                 330

tct gca gtc cct tat tta ggt tgt tgg tta tgt atg atc ctg tcg ggt     1121
Ser Ala Val Pro Tyr Leu Gly Cys Trp Leu Cys Met Ile Leu Ser Gly
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caa gct gct gac aat tta agg gca aga tgg aat ttt tca act ctg tgg     1169
Gln Ala Ala Asp Asn Leu Arg Ala Arg Trp Asn Phe Ser Thr Leu Trp
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gtt cga aga gtt ttt agc ctt ata ggg atg att gga cct gcg ata ttc     1217
Val Arg Arg Val Phe Ser Leu Ile Gly Met Ile Gly Pro Ala Ile Phe
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ctg gtt gcc gca gga ttt ata ggc tgt gat tat tcc ttg gct gtt gca     1265
Leu Val Ala Ala Gly Phe Ile Gly Cys Asp Tyr Ser Leu Ala Val Ala
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ttc cta acc ata tca aca acc ctg gga ggc ttt tgc tct tct gga ttt     1313
Phe Leu Thr Ile Ser Thr Thr Leu Gly Gly Phe Cys Ser Ser Gly Phe
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ggc atc aca aat acc ttt gcc act att cct gga atg att ggg ccc atc     1409
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Tyr Glu Cys Ala Glu His Ser Ala Pro Ile Lys Val Leu His Asn Gln
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Thr Gly Lys Lys Tyr Arg Trp Asp Ala Glu Thr Gln Gly Trp Ile Leu
            100                 105                 110

Gly Ser Phe Phe Tyr Gly Tyr Ile Ile Thr Gln Ile Pro Gly Gly Tyr
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Val Ala Ser Arg Ser Gly Gly Lys Leu Leu Leu Gly Phe Gly Ile Phe
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Ala Thr Ala Ile Phe Thr Leu Phe Thr Pro Leu Ala Ala Asp Phe Gly
145                 150                 155                 160

Val Gly Ala Leu Val Ala Leu Arg Ala Leu Glu Gly Leu Gly Glu Gly
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Val Thr Tyr Pro Ala Met His Ala Met Trp Ser Ser Trp Ala Pro Pro
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Leu Glu Arg Ser Lys Leu Leu Ser Ile Ser Tyr Ala Gly Ala Gln Leu
        195                 200                 205

Gly Thr Val Val Ser Leu Pro Leu Ser Gly Val Ile Cys Tyr Tyr Met
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Asn Trp Thr Tyr Val Phe Tyr Phe Phe Gly Ile Val Gly Ile Ile Trp
225                 230                 235                 240

Phe Ile Leu Trp Ile Cys Leu Val Ser Asp Thr Pro Glu Thr His Lys
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Thr Ile Thr Pro Tyr Glu Lys Glu Tyr Ile Leu Ser Ser Leu Lys Asn
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Leu Pro Leu Trp Ala Ile Val Val Ala His Phe Ser Tyr Asn Trp Thr
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Phe Tyr Thr Leu Leu Thr Leu Leu Pro Thr Tyr Met Lys Glu Val Leu
305                 310                 315                 320

Arg Phe Asn Ile Gln Glu Asn Gly Phe Leu Ser Ala Val Pro Tyr Leu
                325                 330                 335

Gly Cys Trp Leu Cys Met Ile Leu Ser Gly Gln Ala Ala Asp Asn Leu
            340                 345                 350

Arg Ala Arg Trp Asn Phe Ser Thr Leu Trp Val Arg Arg Val Phe Ser
        355                 360                 365

Leu Ile Gly Met Ile Gly Pro Ala Ile Phe Leu Val Ala Ala Gly Phe
    370                 375                 380

Ile Gly Cys Asp Tyr Ser Leu Ala Val Ala Phe Leu Thr Ile Ser Thr
385                 390                 395                 400

Thr Leu Gly Gly Phe Cys Ser Ser Gly Phe Ser Ile Asn His Leu Asp
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Ile Ala Pro Ser Tyr Ala Gly Ile Leu Leu Gly Ile Thr Asn Thr Phe
            420                 425                 430

Ala Thr Ile Pro Gly Met Ile Gly Pro Ile Ile Ala Arg Ser Leu Thr
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Pro Glu Asn Thr Ile Gly Glu Trp Gln Thr Val Phe Cys Ile Ala Ala
    450                 455                 460

Ala Ile Asn Val Phe Gly Ala Ile Phe Phe Thr Leu Phe Ala Lys Gly
465                 470                 475                 480

Glu Val Gln Asn Trp Ala Ile Ser Asp His Gln Gly His Arg Asn
                485                 490                 495
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US006948783B2

(12) **United States Patent**
Hoff

(10) **Patent No.: US 6,948,783 B2**
(45) **Date of Patent: Sep. 27, 2005**

(54) **TENSION ADJUSTMENT MECHANISM FOR A WORK MACHINE**

(75) Inventor: **Brian D. Hoff**, East Peoria, IL (US)

(73) Assignee: **Caterpillar Inc**, Peoria, IL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 276 days.

(21) Appl. No.: **10/067,204**

(22) Filed: **Feb. 7, 2002**

(65) **Prior Publication Data**

US 2003/0122421 A1 Jul. 3, 2003

Related U.S. Application Data

(60) Provisional application No. 60/342,370, filed on Dec. 27, 2001.

(51) **Int. Cl.**[7] **B60B 55/30**
(52) **U.S. Cl.** **305/144**; 305/145
(58) **Field of Search** 305/143, 144, 305/145, 153

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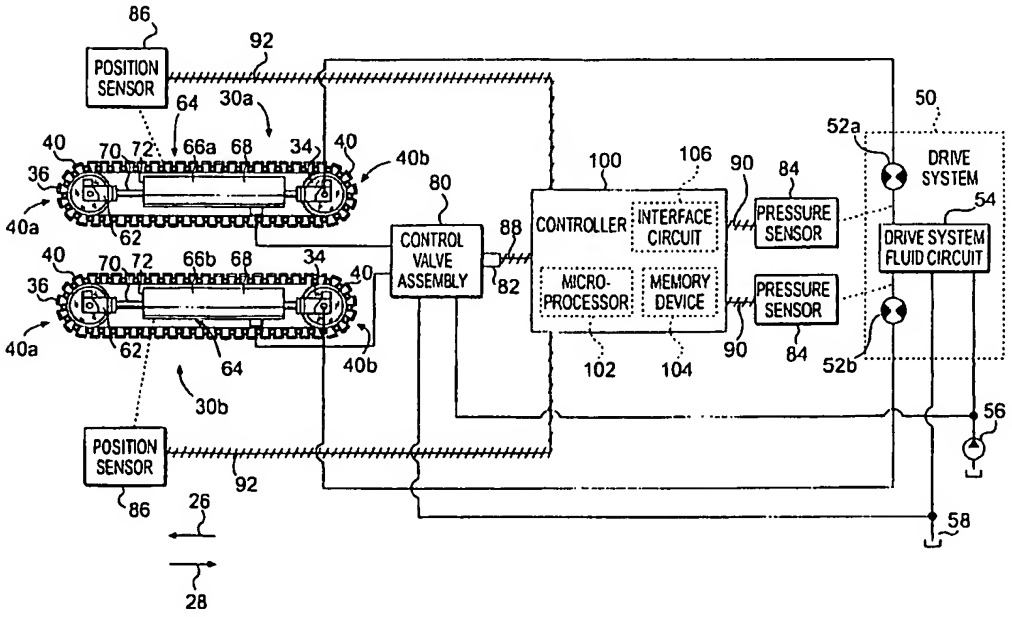
Primary Examiner—Russell D. Stormer
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner

(57) **ABSTRACT**

A method of operating a track-type machine having a drive wheel and an idler. The method includes operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine. The method further includes determining a force to be applied to the idler based on a direction of operation of the drive wheel and applying the force to the idler. The method may include varying the force applied to the idler as a function of a drawbar load of the machine. The method may include sensing a pressure of fluid being used to operate the drive wheel, wherein the force is determined based on the sensed pressure of fluid being used to operate the drive wheel. The method may include determining a force to be applied to the idler by selecting a recoil curve, sensing a position of the idler, and selecting the force to be applied based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve. The recoil curve may be selected from a plurality of recoil curves.

20 Claims, 5 Drawing Sheets



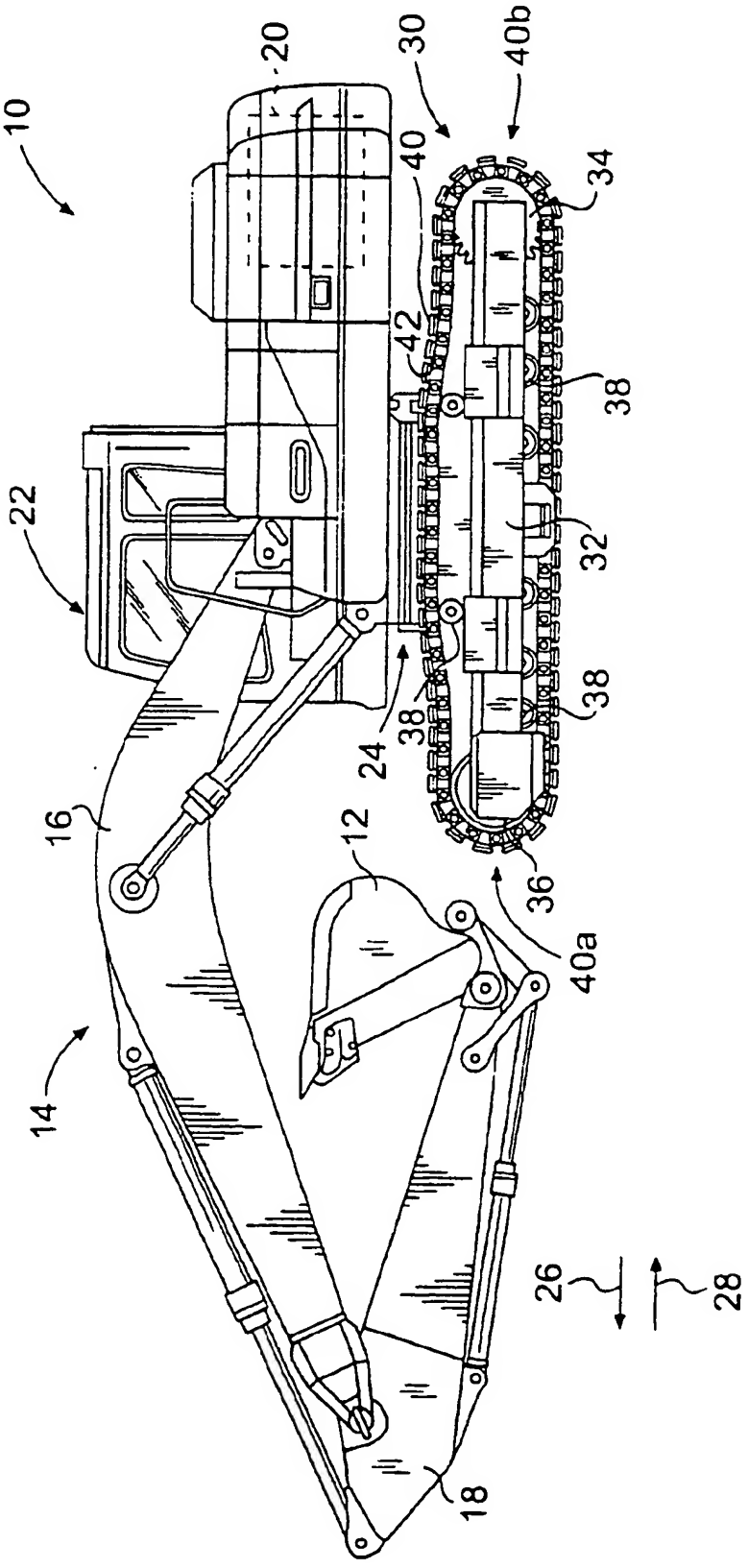


FIG. 1

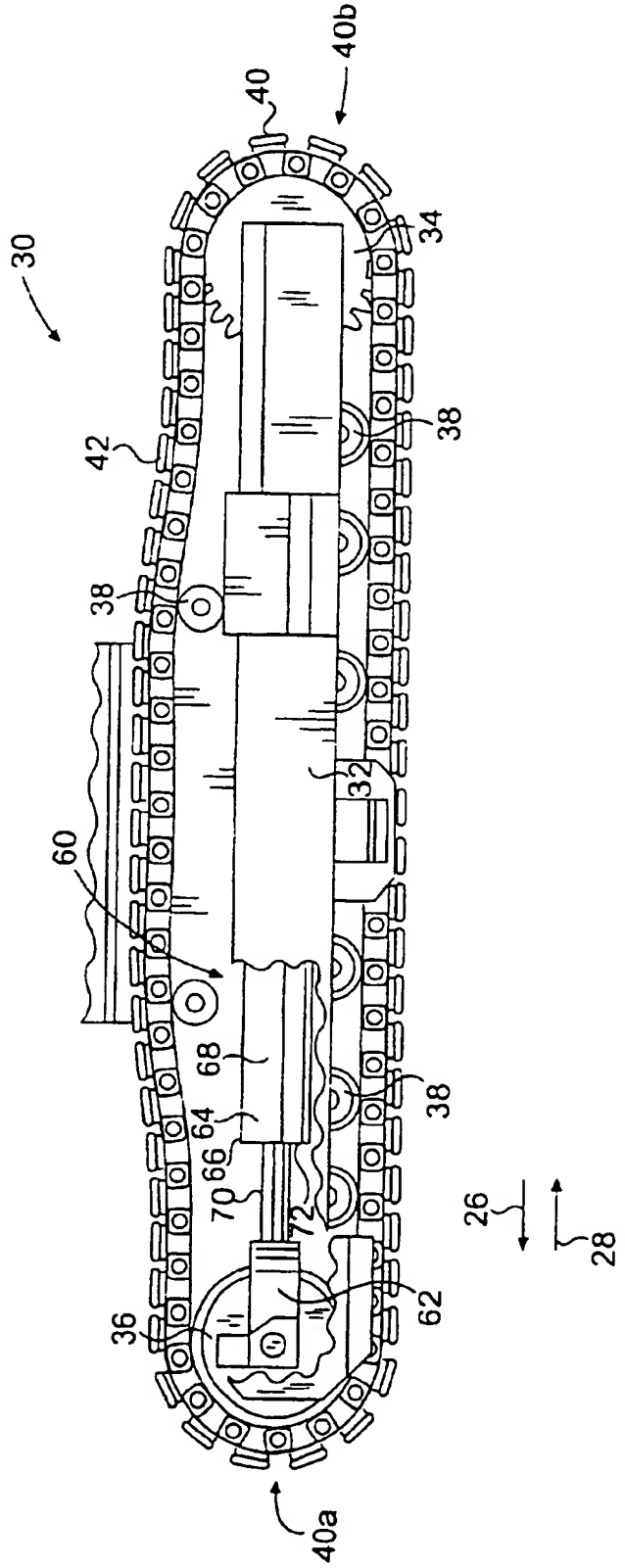
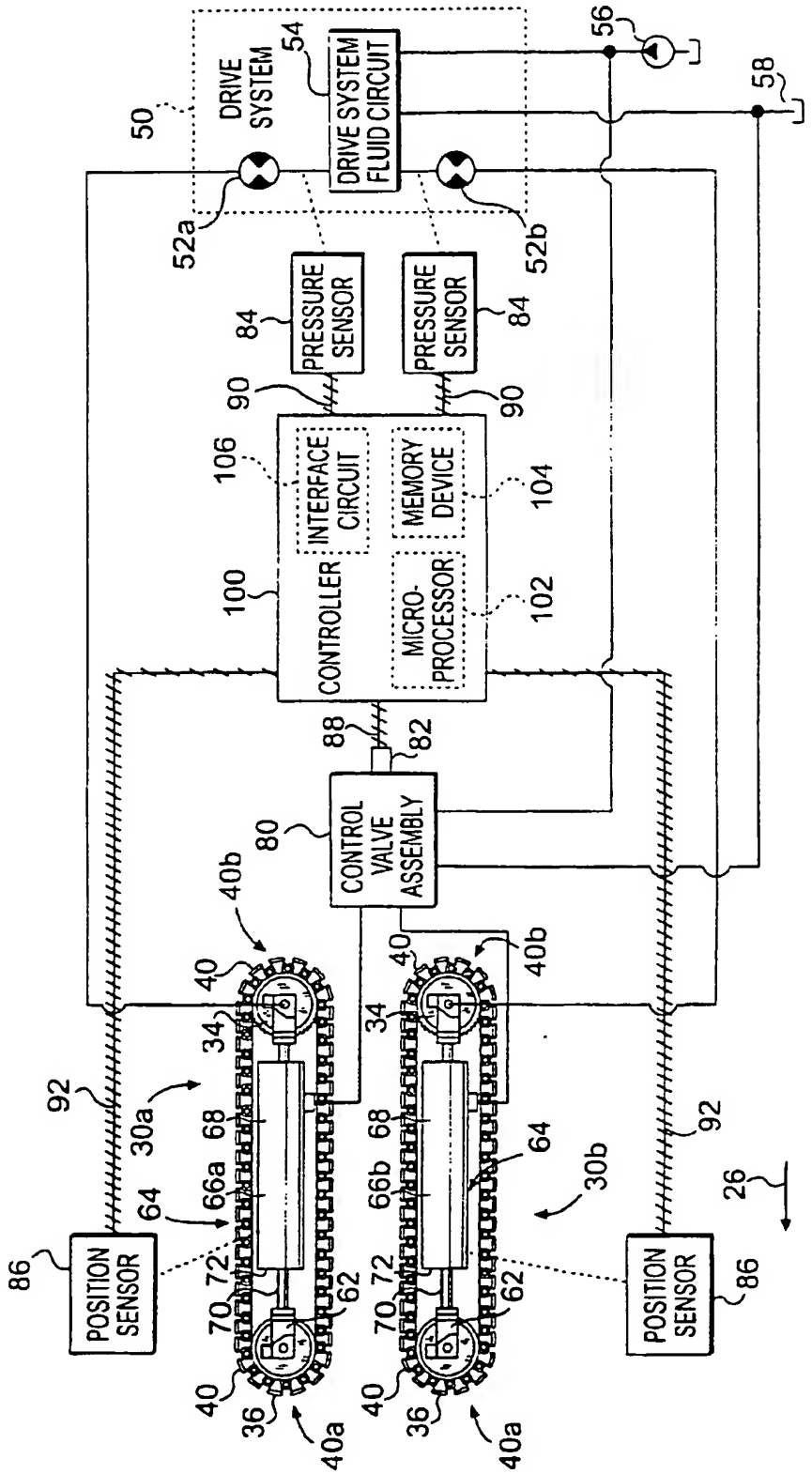


FIG. 2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50
DRIVE SYSTEM FLUID CIRCUIT
54
56
58
52a
52b
PRESSURE SENSOR
84
PRESSURE SENSOR
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CONTROLLER
100
INTERFACE CIRCUIT
106
MEMORY DEVICE
104
MICRO-PROCESSOR
102
88
82
CONTROL VALVE ASSEMBLY
80
40b
40
40
40b
34
34
92
30a
68
68
64
66a
66b
64
30b
72
72
70
70
62
62
86
POSITION SENSOR
POSITION SENSOR
86
36
36
40a
40a
26
28
92

FIG. 3

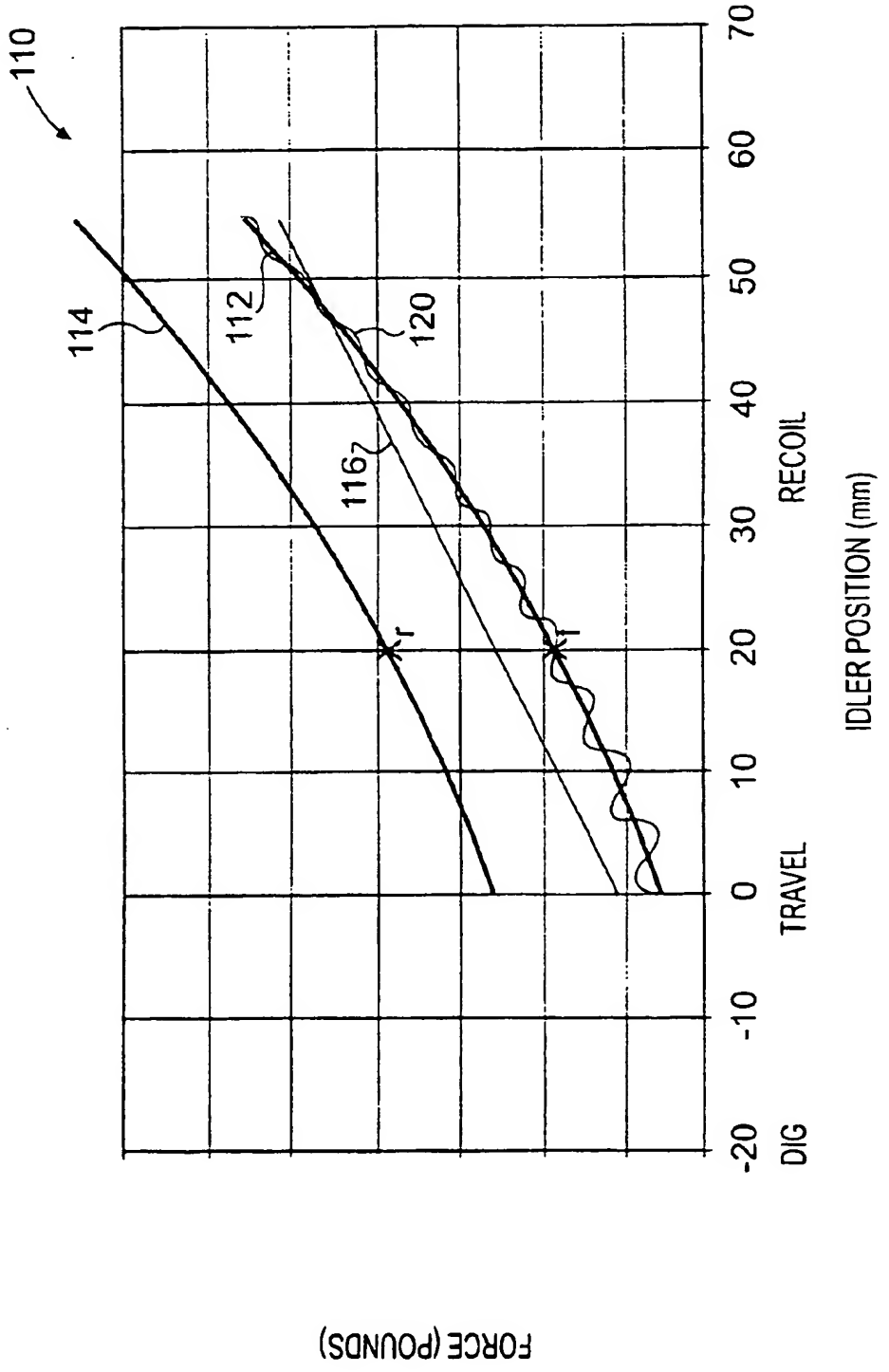

110
114
112
120
116
r
r
70
60
50
40
30
20
10
0
-10
-20
RECOIL
TRAVEL
DIG
IDLER POSITION (mm)
FORCE (POUNDS)

FIG. 4

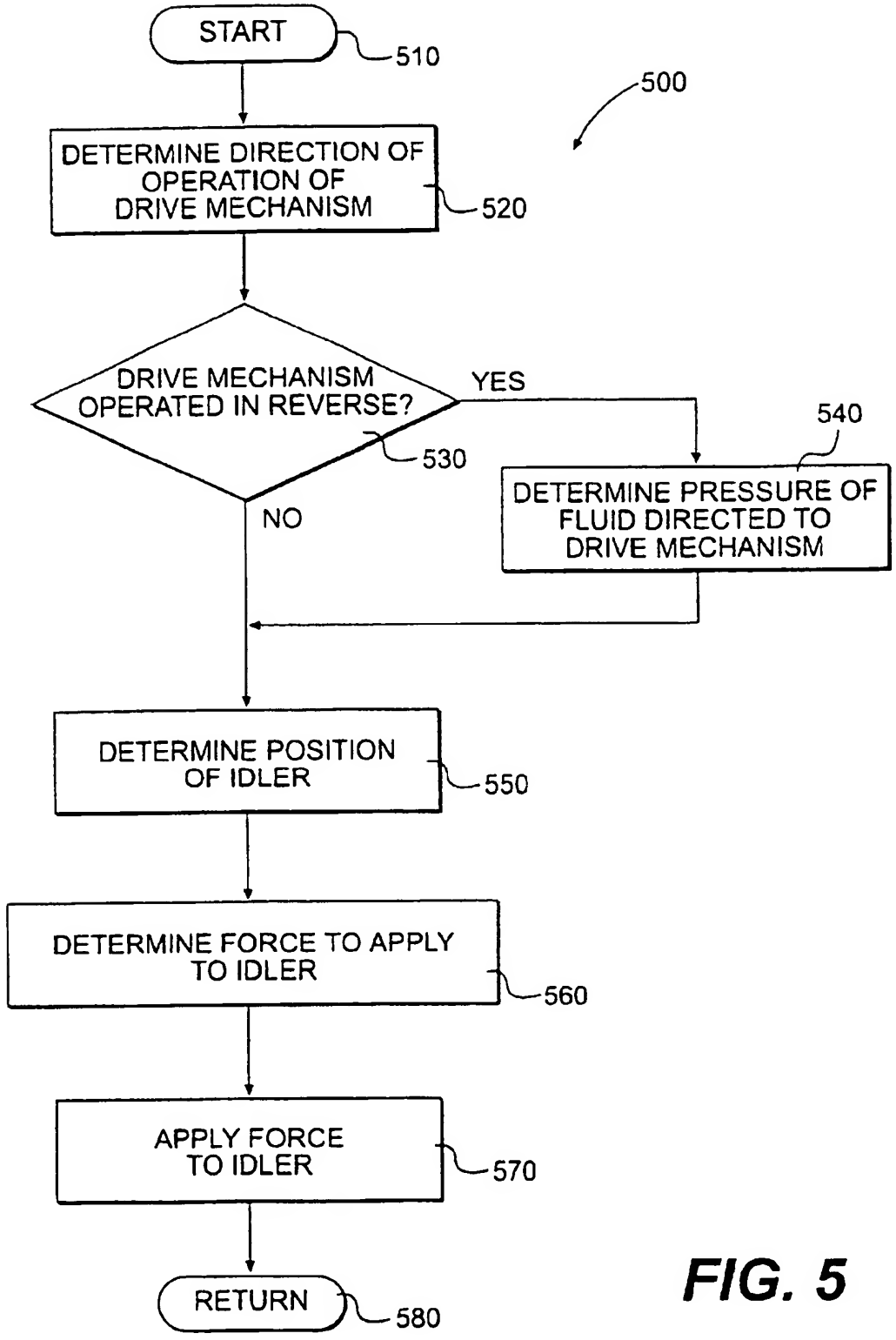

START
510
500
DETERMINE DIRECTION OF OPERATION OF DRIVE MECHANISM
520
DRIVE MECHANISM OPERATED IN REVERSE?
530
YES
NO
540
DETERMINE PRESSURE OF FLUID DIRECTED TO DRIVE MECHANISM
DETERMINE POSITION OF IDLER
550
DETERMINE FORCE TO APPLY TO IDLER
560
APPLY FORCE TO IDLER
570
RETURN
580

FIG. 5

TENSION ADJUSTMENT MECHANISM FOR A WORK MACHINE

The present application claims priority to U.S. Provisional Application Ser. No. 60/342,370, filed Dec. 27, 2001, entitled TENSION ADJUSTMENT MECHANISM FOR A WORK MACHINE, with inventor of Brian D. Hoff, which is incorporated herein by reference.

TECHNICAL FIELD

This invention relates generally to a tension adjustment mechanism for a tracked work machine and, more particularly, to a method of providing a variable force to the idler of the machine based on the direction of operation.

BACKGROUND

A work machine, such as a track-type tractor or excavator, is typically supported and propelled by a pair of undercarriage assemblies. Each of the pair of undercarriage assemblies includes an endless track chain having a plurality of interconnected articulating components or links. Each undercarriage assembly typically also includes a drive wheel or sprocket and one or more idler wheels. The track chain is advanced around the drive sprocket and the one or more idler wheels.

During operation of the work machine, it is necessary to maintain tension on the track chain in order to keep the chain from derailing from the drive wheel or sprocket or the idler wheel. In order to maintain tension on the track chain, a tension adjustment mechanism such as a hydraulic cylinder or coiled spring is often included in the undercarriage assembly.

With regard to excavators, it is generally desirable to have the track chain relatively taut during performance of a digging or other type of work operation in order to prevent wear on the components associated with the undercarriage assembly and to provide a more stable work platform. A relatively taut track chain helps prevent the excavator from rolling back and forth within the interior of the track chain as a result of recoil forces generated during performance of the work operation. Hence, a relatively high tension level is desirably maintained on the track chains of excavators during a work operation, even though it is known that use of such a high tension level increases the rate at which components associated with the undercarriage assembly wear, especially during travel. To create tension on the track chain, the hydraulic cylinder or the coiled spring of the tension adjustment mechanism urges the idler wheel away from the drive wheel or sprocket, increasing the dimension of the undercarriage assembly which the track chain must encircle.

In contrast, it is generally desirable to have the track chain relatively loose during advancement or travel of an excavator. By loosening or otherwise decreasing tension on the track chain, wear on the components associated with the undercarriage assembly is reduced. This increases the efficiency and even the useful life of the excavator. To reduce tension in the track chain, the hydraulic cylinder or coiled spring of the tension adjustment mechanism moves the idler wheel toward the drive wheel or sprocket a certain incremental amount.

The tension adjustment mechanism also provides a recoil function in the track chain, accommodating temporary forces on the track such as when a rock or the like is ingested between the track and the wheels during advancement of the excavator. In these instances, the idler wheel is permitted to recoil toward the drive sprocket in order to accommodate the extra length the track must encircle in order to accommodate the rock without breaking.

When traveling in one direction, the rotation of the drive wheel or sprocket pulls on the top flight of the track chain, exerting a recoil force on the idler wheel. During travel in the opposite direction, the drive wheel or sprocket pulls on the bottom flight of the track chain which, because the bottom flight bears the weight of the machine against the ground, does not significantly transmit that force through the track chain to the idler wheel. Conventional track tension/recoil systems have a tensioning mechanism for varying track tension based on dig and travel requirements, and accordingly are not optimized for either.

U.S. Pat. No. 6,249,994 ("the '994 patent") discloses a tensioning mechanism which decreases track tension by a predetermined amount when the machine is traveling. The '994 patent discloses detecting an increase in drive pressure when the machine goes into its travel mode (because fluid is diverted from a work implement to the drive system) and then decreasing tension on the track chain in response to the detection of the increase in fluid drive pressure. Conversely, the '994 patent discloses detecting a decrease in drive pressure when the machine goes into its work mode (because fluid is diverted from the drive system to the work implement) and then increasing tension on the track chain in response to the detection of the increase in fluid drive pressure. The '994 patent does not disclose, however, differentiating between directions of travel and the drive force required to achieve travel.

In addition, conventional work machines do not effectively compensate for the advancement of the excavator under high drawbar loads, which is a common cause of "sprocket jumping," a condition where a bushing on the track chain slips over a tooth on the drive sprocket. Sprocket jumping has a detrimental effect on the wear of the components of the undercarriage assembly and on the hydraulic drive motor as it reflects large spikes in the pressure going into the drive motor. In addition, the recoil force created by the drive sprocket on the idler wheel during travel in one direction increases in proportion to the energy required to move the machine (referred to as drawbar load), sometimes moving the idler wheel too close to the drive sprocket under high drawbar loads.

The present invention is directed to solving one or more of the problems or disadvantages set forth above of current work machines.

SUMMARY OF THE INVENTION

The present invention provides a method of operating a track-type machine having a drive wheel and an idler. The method includes operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine. The method further includes determining a force to be applied to the idler based on a direction of operation of the drive wheel and applying the force to the idler. The method may include varying the force applied to the idler as a function of a drawbar load of the machine. The method may include sensing a pressure of fluid being used to operate the drive wheel, wherein the force is determined based on the sensed pressure of fluid being used to operate the drive wheel. The method may include determining a force to be applied to the idler by selecting a recoil curve, sensing a position of the idler, and selecting the force to be applied based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve. The recoil curve may be selected from a plurality of recoil curves.

The present invention also provides a work machine that includes a source of pressurized fluid, a fluid reservoir, a drive track, an idler, a drive wheel, an actuator, a valve assembly, and a controller. The drive wheel is operable to advance the drive track around the drive wheel and the idler. The actuator is mechanically coupled to the idler and is operable to increase and decrease a force being applied to the idler. The valve assembly is operable to control fluid flow from the source of pressurized fluid to the actuator and from the actuator to the fluid reservoir. The controller is configured to operate the valve assembly to apply a force to the idler based on a direction of operation of the drive wheel.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a side elevational view of an excavator which incorporates an exemplary embodiment of the present invention therein;

FIG. **2** is an enlarged, partially cutaway side elevational view of the undercarriage assembly of the excavator of FIG. **1**;

FIG. **3** is a schematic illustration of a track tensioning assembly according to an exemplary embodiment of the present invention;

FIG. **4** is a graph illustrating the recoil response of an exemplary embodiment of the present invention; and

FIG. **5** is a block diagram illustrating a method of determining a force to be applied to an idler of a track-type work machine based on the direction of operation of the machine according to the present invention.

DETAILED DESCRIPTION

The invention as described below is applied to a hydraulic excavator. It should be appreciated that the present invention may be applied to any type of work machine having an endless track, such as a rubber belt or drive track chain, including, for example, track-type tractors, loaders, and military vehicles.

FIG. **1** illustrates a track-type work machine, for example, a hydraulic excavator **10**, that is utilized to perform numerous work functions, such as digging and material movement. The excavator **10** may include a number of work implements, such as, for example, a hydraulically-powered bucket assembly **12**, which is secured to an end of a boom assembly **14** having a boom arm **16** and a stick assembly **18**. The excavator **10** further includes an engine such as, for example, a diesel engine **20**, for providing the motive power for both advancing the excavator **10** and operating the bucket assembly **12** and the boom assembly **14**.

The excavator **10** also includes a pair of undercarriage assemblies **30** (see FIG. **3**), although only one undercarriage assembly **30** is shown in FIGS. **1** and **2**. Each undercarriage assembly **30** generally includes a frame assembly **32**, a drive mechanism **34**, an idler wheel **36**, and a number of midroller assemblies **38**. For each undercarriage assembly **30**, a drive track **40**, such as, for example, an endless track chain, may be driven by the drive wheel **34** so as to be advanced around the idler wheel **36** and each of the midroller assemblies **38**, thereby providing the motive power for advancing the excavator **10**. It should be appreciated that drive mechanism **34** may comprise a drive wheel which is frictionally engaged with the drive track **40** or a drive sprocket which is mechanically engaged with the drive track chain **40**. In one embodiment, the drive wheel **34** is positioned at a first end **40***b* of the assembly **30**, while the idler wheel **36** is positioned at a second and opposite end **40***a* of the assembly **30**. As shown in FIG. **1**, in an exemplary embodiment, the idler wheel **36** is positioned at the "front" end of the excavator **10** relative to a cab **22** (discussed below), while the drive wheel **34** is positioned at the "rear" end of the excavator **10** relative to the cab **22**.

FIG. **3** is a schematic illustration of a track tensioning assembly according to an exemplary embodiment of the present invention. To advance the excavator **10**, mechanical output from the engine **20** (see FIG. **1**) is transmitted to the drive wheels **34** via a hydraulic drive system **50** having one or more hydraulic drive motors **52**. Each hydraulic drive motor **52** drives at least one of the drive wheels **34** to advance the drive track **40** and, hence, the excavator **10**. As shown in FIG. **3**, hydraulic drive motor **52***a* drives a drive wheel **34** associated with one undercarriage assembly **30***a* and hydraulic drive motor **52***b* drives a second drive wheel **34** associated with the other undercarriage assembly **30***b*. Through a drive system fluid circuit **54**, each hydraulic motor **52***a*, **52***b* of the hydraulic drive system **50** is fluidly coupled with at least one source of pressurized fluid **56**, such as, for example, a high-pressure pump (see FIG. **3**). The drive system fluid circuit **54** supplies pressurized hydraulic fluid to the hydraulic motors **52***a*, **52***b*.

As shown in FIG. **1**, the excavator **10** also includes the cab **22** that is provided to enclose or otherwise house the devices associated with the excavator **10**, which are utilized by an operator during operation of the excavator **10**. In particular, the cab **22** houses an operator seat (not shown) and a number of control devices such as a control lever assembly (not shown) and a foot pedal assembly (not shown). The cab **22** is positioned on the undercarriage assembly **30** of the excavator **10** on a swivel **24**. The swivel **24** allows the cab **22** to be turned in both the clockwise and counterclockwise directions relative to the pair of undercarriage assemblies **30***a*, **30***b* (see FIG. **3**).

In addition to the engine **20**, other components of the excavator **10** may be positioned above the swivel **24**. In one embodiment, the at least one fluid source **56** may be positioned above the swivel **24**. In another embodiment, one or more return tanks or fluid reservoirs **58** (see FIG. **3**) may be positioned above the swivel **24**. As shown in FIG. **3**, in an exemplary embodiment, a single fluid source **56** and a single reservoir **58** are fluidly coupled with both the drive system **50** that supplies hydraulic fluid to the motors **52***a*, **52***b* and a control valve assembly **80** (discussed below) that supplies hydraulic fluid to a recoil assembly **64** (discussed below) of each of the undercarriage assemblies **30***a*, **30***b*. One skilled in the art understands that the components positioned above the swivel **24** are connected with the components of the undercarriage assembly **30** through various conventional fluid and electrical lines (not shown) that travel through the swivel **24** or through wireless communications (such as a radio) (not shown). Typically, the hydraulic motors **52***a*, **52***b* of the hydraulic drive system **50** (not shown in FIG. **1**) are positioned below the swivel **24**.

As shown in more detail in FIG. **2**, each undercarriage assembly **30** includes a track tensioning assembly **60**. The track tensioning assembly **60** is configured to (1) provide a relative taut track configuration in order to minimize wear and prevent the excavator **10** from rolling back and forth during a work operation and (2) loosen the tension on the drive track **40** during advancement of the excavator **10** in order to decrease undercarriage component wear.

The track tensioning assembly **60** includes a recoil assembly **64** having a yoke **62** secured thereto. As shown in FIGS. **2** and **3**, the idler wheel **36** is rotatably coupled to the yoke

62. Movement of the yoke **62** and hence the idler wheel **36** away from the drive wheel **34** (i.e., in the general direction of arrow **26** of FIGS. **1–3**) increases tension of the drive track **40**. Conversely, movement of the yoke **62** and hence the idler wheel **36** toward the drive wheel **34** (i.e., in the general direction of arrow **28** of FIGS. **1–3**) decreases tension of the drive track **40**.

The recoil assembly **64** includes an actuator that generally includes a cylinder that defines a chamber or housing, and a rod and/or a piston that are positioned within the housing. The components of the recoil assembly **64** are assembled together such that one component is fixed to the frame assembly **32** of the undercarriage assembly **30**, while another component is moveable relative to the first component and is connected with the idler wheel **36** (through the yoke **62** as noted above) so as to urge that idler wheel **36** to increase and decrease tension on the drive track **40**, respectively.

In one exemplary embodiment, as shown in FIGS. **2** and **3**, each recoil assembly **64** may include an actuator, which are shown (in FIG. **3**) as a right hydraulic cylinder **66***a* and a left hydraulic cylinder **66***b* for the pair of undercarriage assemblies **30***a*, **30***b*, respectively. The hydraulic cylinders **66***a*, **66***b* each have a fixed cylinder housing **68** having a moveable rod **70** extending therefrom. The rod **70** extends from a sealed opening **72** defined in the cylinder housing **68**. In one exemplary embodiment, a first end of the rod **70** is secured to a piston (not shown) within the cylinder housing **68**. A second end of each rod **70** is secured to the yoke **62** associated with the idler wheel **36**. Extension of the rods **70** (i.e., movement of the rods **70** in the general direction of arrow **26**) causes corresponding movement of the idler wheels **36**, thereby increasing tension on the drive tracks **40**. Conversely, retraction of the rods **70** (i.e., movement of the rods **70** in the general direction of arrow **28**) causes corresponding movement of the idler wheels **36**, thereby decreasing tension on the drive tracks **40**.

In an alternative embodiment (not shown), the rod is fixed to the frame assembly of the excavator, and the cylinder housing is moveable relative to the fixed rod. In this exemplary embodiment, the cylinder housing is secured to the yoke such that extension of the cylinder housing causes corresponding movement of the idler wheel through the yoke. An advantage of this embodiment is that the seal between the rod and the cylinder housing is positioned within the cylinder housing, in a more protected environment. Generally, when the idler wheel kicks up debris from the round, the seal is not positioned where the debris is kicked up. In an alternative of this embodiment, the recoil assembly could be a single acting cylinder having a single port, and the port could be in the rod.

The disclosed system provides a method of operating a track-type machine, such as an excavator **10**, by determining an appropriate force to be applied to the idler wheel **36** based on a direction of operation of the drive wheel **34** and then applying the appropriate force to the idler wheel **36** to achieve tension on the drive track **40**. Determining the appropriate force to be applied to the idler wheel **36** may include determining a first force when the drive wheel **34** is operated in a first direction and determining a second force when the drive wheel **34** is operated in a second direction, where the second direction is opposite the first direction.

In one embodiment, the first direction is in the direction from the drive wheel **34** toward the idler wheel **36** and the second direction is in the direction from the idler wheel **36** toward the drive wheel **34**. In the embodiment where the idler wheel **36** is positioned at the front end (shown as **40***a* in FIGS. **1–3**) of the excavator **10** and the drive wheel **34** is positioned at the rear end (shown as **40***b* in FIGS. **1–3**) of the excavator **10**, the first direction is the forward direction **26** and the second direction is the rearward direction **28**.

FIG. **5** illustrates a block diagram **500** of an exemplary operation of determining a force to be applied to an idler and applying the force to the idler to achieve a tension on the drive track. The exemplary operation commences with step **510**. Then, in step **520**, it is determined in which direction the drive mechanism is being operated. If, in step **530**, the drive mechanism is being operated in the forward direction, control then proceeds to step **550** where the position of the idler wheel is determined. If, in step **530**, the drive mechanism is being operated in the reverse direction, control then proceeds to step **540**, where the fluid pressure to the drive mechanism is determined. Control then proceeds to step **550** where the position of the idler is determined.

After step **550**, control proceeds to step **560** where the appropriate force to apply to the idler is determined. While traveling in the forward direction, the appropriate force to be applied to the idler is based on the determined position of the idler. While traveling in the reverse direction, the appropriate force to be applied to the idler is based on the determined pressure of fluid to the drive mechanism and the determined position of the idler. If the machine is not traveling, i.e., is stopped, then the force applied to the idler is generally a single force applied to the idler so as to maintain a tension on the drive track. This single force may be higher than the force applied to the idler wheel when the machine is traveling in the forward direction and when the machine is traveling in the reverse direction. This is because when the machine is stopped, the machine is often in a work mode, when the tension on the drive track should be higher than when the machine is traveling.

Control proceeds to step **570** where the appropriate force is applied to the idler wheel. Control then continues to step **580** where the control is returned to step **510**.

In one embodiment, the method of determining the force to be applied to the an idler wheel **36** and then applying the force to the idler wheel **36** to achieve tension on the drive track **40** includes utilizing one or more recoil curves, such as curves **112** and **114** shown in the graph of FIG. **4**. The x-axis of the graph is the displacement (in millimeters) of the idler wheel **36**. The y-axis of the graph is the force (pounds) that will be exerted on the idler wheel **36** to control recoil. The graph illustrates two curves, **112** and **114**, a line **116**, and a wavy line **120**. The curve **112** illustrates an appropriate recoil response when the excavator **10** is traveling in the forward direction **26**. The wavy line **120** illustrates an actual recoil response. The actual recoil response **120** is near the curve **112** but does not necessarily fall directly on curve **112**. The curve **114** illustrates one of a plurality of recoil responses when the excavator **10** is traveling in the rearward direction **28**. The line **116** illustrates the recoil response for a prior art work machine that uses a coiled spring for a tension adjustment mechanism.

While the curve **112** and the curve **114** have the same general shape, the curve **114** is translated up on the y-axis because more force needs to be applied on the idler wheel **36** to counteract the force of the drive wheel **34** pulling on the idler wheel **36** during travel in the rearward direction **28**. As discussed above, during travel in the rearward direction **28**, the drive wheel **34** pulls the top flight **42** of the drive track **40** around the idler wheel **36**. When the idler wheel **36** is positioned at the front end of the machine, this force pulls

the idler wheel **36** toward the drive wheel **34**, which aids the recoil function.

The curve **112**, representing a desired recoil response curve when traveling in the forward direction **26**, generally is a single curve for a single work machine. This is because, when traveling in the forward direction **26**, the drive wheel **34** feeds the drive track **40** to the idler wheel **36** along the top flight **42**. Thus, there is no pulling force on the idler wheel **36** by the drive wheel **34** to counteract.

In contrast, the curve **114**, representing a desired recoil response curve when traveling in the rearward direction **28**, may be one of a plurality of appropriate recoil response curves. The force exerted on the idler wheel **36** by the drive wheel **34** may vary depending on the drawbar load while the work machine is traveling in the rearward direction. Accordingly, there are a plurality of recoil response curves for a work machine traveling in the rearward direction that may be obtained through the present invention. Because a plurality of appropriate recoil response curves are provided for travel in the rearward direction, a work machine equipped with the present invention would operate equally well in the forward and rearward directions with high and low drawbar loads.

To graph the recoil response curves **112** and **114**, data points may be plotted based on operating characteristics of the machine including the geometry of the undercarriage assembly, for example, the amount of space for a bushing to jump off the drive wheel and the wear on the track chain. The data points of the recoil response curves **112** and **114** may also be based on the drawbar load or environment conditions, such as the underfoot condition. The drawbar load is generally any force that the work machine has to overcome to move in a direction and includes, for example, the gross vehicle weight of the work machine, as well as the gross vehicle weight of any attachments attached to the work machine and any slope on which the work machine is traveling. The underfoot condition refers to the surface on which the work machine is traveling and includes pavement, soft dirt, mud, clay, and the like. Once the data points of the recoil response curves **112** and **114** are plotted on a graph, an equation may be determined that best fits those data points. This equation may be inserted as part of the algorithm that is part of the code (that is stored in a memory device **104** discussed below) that is utilized to vary the force applied to the idler wheel **36** based on the recoil response curves **112** and **114**.

When the excavator **10** is traveling in the rearward direction **28**, the fluid pressure to the drive motor **52***a* is proportional to a force pulling on the idler wheel **36** by the drive wheel **34** of the right undercarriage assembly **30***a* and, similarly, the fluid pressure to the drive motor **52***b* is proportional to a force pulling on the idler wheel **36** by the drive wheel **34** of the left undercarriage assembly **30***b*. For each of the undercarriage assemblies **30***a*, **30***b*, once the fluid pressure to its drive motor **52** (also referred to as "the drive pressure") is known, the fluid pressure to its hydraulic cylinder **66** may be increased to counteract the force that its drive wheel **34** exerts on its idler wheel **36** during travel in the rearward direction that tends to cause recoil. For each of the undercarriage assemblies **30***a*, **30***b*, the increase of fluid pressure to its hydraulic cylinder **66** creates another force that is applied to its idler wheel **36** in the direction **26**, i.e., away from its rear drive wheel **34**, to counteract the effect of the force of the drive wheel **34** pulling on the idler wheel **36**.

The recoil response of the present invention is such that the external force required to cause recoil of the idler wheel **36** is the same, whether the machine is traveling forward or reverse, with high or low drawbar loads. The force applied to counteract recoil varies according to whether the machine is traveling in the forward direction **26** or the rearward direction **28**.

It should also be appreciated that the amount of the drawbar load is proportional to the drive pressure because the fluid pressure to the drive motors **52***a*, **52***b* would be increased if the drawbar load increased, in order to ensure that the machine may overcome the weight of the machine and/or any attachments and be able move in a given direction. In addition, as noted above, when the machine is traveling in the rearward direction **28**, the fluid pressure to the drive motors **52** is proportional to the force pulling on the idler wheel **36**. Accordingly, the drive pressure is proportional to both the amount of the drawbar load and the amount of the force pulling on the idler wheel **36** to affect recoil when the machine is traveling in the rearward direction **28**.

As shown in FIG. **3**, in one exemplary embodiment, a controller **100** communicates with an electrically-actuated control valve assembly **80**, one or more pressure sensors **84**, and one or more position sensors **86** in order to maintain tension on each drive track **40** of each undercarriage assembly **30***a*, **30***b*. For example, the controller **100** may be utilized to provide an appropriate recoil response (such as curve **112** (for forward direction **26**) and curve **114** (for rearward direction **28**) shown in FIG. **4**) for the excavator **10**. Generally, the controller **100** may receive signals from the position sensors **86** representing the positions of the hydraulic cylinders **66***a*, **66***b* and signals from the pressure sensors **84** representing the fluid pressure to each of the hydraulic motors **52***a*, **52***b* of the hydraulic drive system **50**. Utilizing these signals, as well as an algorithm that includes at least one recoil response curve, the controller **100** may determine whether fluid needs to be supplied to or drained from the hydraulic cylinders **66***a*, **66***b*. Upon a signal from the controller **100**, the control valve assembly **80** may be utilized to either supply fluid to or drain fluid from the hydraulic cylinders **66***a*, **66***b* in order to obtain a level of tension based on the appropriate recoil response.

The control valve assembly **80** controls actuation of the hydraulic cylinders **66***a*, **66***b* in order to increase or decrease tension on its corresponding drive track **40**. The control valve assembly **80** is electrically coupled to the controller **100**. In one exemplary embodiment, a solenoid **82** of the control valve assembly **80** is electrically coupled to the controller **100** via a signal line **88**. To increase fluid pressure in the hydraulic cylinders **66***a*, **66***b*, fluid is supplied to the hydraulic cylinders **66***a*, **66***b* from the fluid source **56** through the control valve assembly **80**. To decrease fluid pressure in the hydraulic cylinders **66***a*, **66***b*, fluid is drained from the hydraulic cylinders **66***a*, **66***b* to the fluid reservoir **58** through the control valve assembly **80**.

In one exemplary embodiment, the control valve assembly **80** includes an independent metering valve (IMV) assembly. The IMV assembly may be operated to fluidly couple the hydraulic cylinders **66***a*, **66***b* so as to increase or decrease fluid pressure in the hydraulic cylinders **66***a*, **66***b* to increase or decrease, respectively, tension on the drive track **40**. The IMV assembly may be an electrically-actuated valve assembly that includes a pressure sensor **84** therein.

The one or more pressure sensors **84** are utilized to sense pressure in one or more fluid lines. In an exemplary embodiment, one pressure sensor **84** senses the fluid pressure to the hydraulic motor **52***a* (that drives the drive wheel **34** for the undercarriage assembly **30***a*), while a second

pressure sensor **84** senses the fluid pressure to the hydraulic motor **52***b* (that drives the drive wheel **34** for the undercarriage assembly **30***b*). Each pressure sensor **84** may be electrically coupled to the controller **100** via a signal line **90**. Thus, in the embodiment including two pressure sensors **84**, output signals generated by the pressure sensors **84** are communicated to the controller **100** via a pair of signal lines **90**.

The one or more position sensors **86** may be located such that they can monitor the position of a number of undercarriage components relative to one another. At least one of the position sensors **86** is provided to sense the position of one rod **70** relative to its corresponding housing **68** of one of the hydraulic cylinders **66***a*, **66***b*. In one exemplary embodiment, two position sensors **86** are provided, each to sense the position of each rod **70** relative to its corresponding housing **68** of each of the hydraulic cylinders **66***a*, **66***b*. The position sensors **86** may be provided as any type of sensor which is capable of sensing the position of the rods **70**. It should be appreciated that the position of the idler wheels **36** may be ascertained from the position of the rod **70** relative to its corresponding housing **68**. In another exemplary embodiment, at least one of the position sensors **86** may be provided to sense the position of at least one of the idler wheels **36**. For example, the position sensors may be magnetostrictive position sensors that are part of the hydraulic cylinders **66***a*, **66***b* or linear displacement transducers.

Each position sensor **86** may be electrically coupled to the controller **100** via a signal line **92** or, in the alternative, via wireless communication (not shown). Thus, in the embodiment including two position sensors **86** for sensing each of idler wheels **36** of both undercarriage assemblies **30***a*, **30***b*, output signals generated by the position sensors **86** are communicated to the controller **100** via a pair of signal lines **92**. Such output signals may be generated and thereafter communicated by the position sensors **86** in numerous forms. For example, the position sensors **86** may generate output signals in the form of an analog DC voltage, or in the form of a signal utilizing current-to-pulse signal timing or pulse width modulation.

The controller **100** includes electrical components commonly found in other work machine controllers, such as a microprocessor **102**, a memory device **104**, and an interface circuit **106**. The controller **100** may be a dedicated controller for controlling the components shown in FIG. **3**. In the alternative, the controller **100** may be integrated into another controller associated with the excavator **10**, such as an engine controller (not shown), transmission controller (not shown), or an implement controller (not shown).

The interface circuit **106** converts the output signals from the one or more pressure sensors **84** and the one or more position sensors **86** into signals that are suitable for presentation to an input of the microprocessor **102**. It should be appreciated that the magnitude of the voltage generated by each pressure sensor **84** is indicative of the hydraulic fluid pressure to one of the hydraulic motors **52***a*, **52***b*, while the magnitude of the voltage generated by each position sensor **86** is indicative of the position of one of the rods **70** within its corresponding cylinder housing **68** or, more generally, the position of one of the idler wheels **36**.

The interface circuit **106** also converts output signals generated by the microprocessor **102** into signals which are suitable for use by the solenoid **82** associated with the control valve assembly **80**. In particular, the interface circuit **106** may convert the output signals from the microprocessor **102** into an analog actuation pulse which actuates the solenoid **82**, thereby positioning the control valve assembly **80** into one of its actuated positions in order to cause extension or retraction of the hydraulic cylinders **66***a*, **66***b*, as described above. It should be appreciated that the interface circuit **106** may be embodied as a discrete device or a number of devices, or may be integrated into the microprocessor **102**.

The memory device **104** is provided to store the code or set of instructions that are executed by the controller **100** during operation of the track tensioning assembly **60**. For example, the memory device **104** is utilized to store the code containing an algorithm that includes a plurality of appropriate recoil curves, such as a recoil curve **112** (see FIG. **4**) for travel in the forward direction **26** and a plurality of recoil curves **114** (see FIG. **4**) for travel in the rearward direction **28**, for a variety of parameters. Moreover, operation parameters may also be stored in the memory device **104**. The memory device may be embodied as any known memory device, such as RAM and/or ROM devices.

As discussed above, in an exemplary embodiment, the controller **100**, along with the control valve assembly **80**, the pressure sensor(s) **84**, and the position sensor(s) **86**, are utilized to ensure that the recoil response of a work machine is at or near a level of tension based on the desired recoil curves **112** and **114** for that machine. Again, the actual recoil response may not fall directly on curve **112** or **114**, but may fall generally around these curves, such as shown in the wavy line **120** that follows the general shape of curve **112**.

As noted above, there are a plurality of recoil response curves **114** for a single work machine. In one embodiment, the controller **100** first determines which of the available recoil response curves is the appropriate recoil response curve. For example, the controller **100** may select the appropriate recoil response curve **114** based on the reverse drive pressure (the drive pressure to the hydraulic motors **52***a*, **52***b* when the excavator is traveling in the rearward direction **28**) sensed by the pressure sensor **84**, because the reverse drive pressure is proportional to the force pulling on the idler wheel **36**. Thus, the appropriate recoil response curve **114** selected is based on compensating or counteracting for that force pulling on the idler wheel **36**. As discussed above, the appropriate recoil response curve **114** selected is indirectly reflective of the drawbar load and the underfoot condition because each of the available recoil response curves include data points that are reflective of the drawbar load and the underfoot condition.

In an exemplary embodiment, when the reverse drive pressure to the drive motors **52***a*, **52***b* is continuously sensed by pressure sensors **84**, the controller **100** continuously selects an appropriate recoil response curve **114** for each of the undercarriage assemblies **30***a*, **30***b*, respectively. A later selected appropriate recoil response curves **114** may be similar to an earlier curve if conditions are relatively constant or may be quite different if conditions change, such as, for example, traveling on a different surface (a different underfoot condition).

Optionally, applying the appropriate force to the idler wheel **36** based upon a recoil curve **112** or **114** includes sensing a position of the idler wheel **36** to determine the amount of recoil of the idler wheel **36**, plotting the sensed position of the idler wheel **36** on the recoil curve **112** or **114**, and varying the force to the idler wheel **36** based on the recoil curve **112** or recoil curve **114**.

More particularly, the position sensor **86** senses the position of rod **70** within its corresponding housing **68** of at least

one of the hydraulic cylinders 66*a*, 66*b*. In an exemplary embodiment, two position sensors 86 each sense the position of a rod 70 within its corresponding housing 68 of both hydraulic cylinders 66*a*, 66*b*. It should be appreciated that the position of the idler wheel 36 is dependent on the position of the rod 70. Thus, once the position of the rod 70 relative to its corresponding housing 68 is determined, then the position of the idler wheel 36 may be determined or, in other words, the amount of recoil of the idler wheel 36. In the exemplary embodiment, because both hydraulic cylinders 66*a*, 66*b* are being sensed, the amount of recoil of both idler wheels 36 may be determined.

Once the amount of recoil of the idler wheel 36 is inputted into the controller 100, the controller 100 compares the position of the idler wheel 36 to the recoil curve 112 (when the excavator 10 is traveling in the forward direction 26) or the appropriate recoil curve 114 that the controller 100 has selected for that situation (when the excavator 10 is traveling in the rearward direction 28). In the exemplary embodiment, because the amount of recoil of both idler wheels 36 are determined, the positions of both of the idler wheels 36 are compared to the recoil curve 112 or 114 for that undercarriage assembly 30*a*, 30*b*.

For each undercarriage assembly 30*a*, 30*b*, the amount of idler wheel 36 recoil is a position value (on the x-axis) on a graph, such as shown in FIG. 4. Knowing that idler wheel 36 position, it is determined how much to vary the force applied to the idler wheel 36 by determining what the appropriate force on the idler wheel 36 should be based on the recoil curve 112 (when traveling in the forward direction 26) or the appropriate recoil curve 114 (when traveling in the rearward direction 28). For example, if the idler wheel 36 recoil is around 20 mm, then the amount of force that should be applied to the idler wheel 36 is shown as X_f in FIG. 4 during travel in the forward direction 26 and is shown as X_r during travel in the rearward direction 28. In the exemplary embodiment, the amount of force to be applied to the idler wheel 36 is determined for both idler wheels 36 of both undercarriage assemblies 30*a*, 30*b* based on the recoil curve 112 or the appropriate recoil curve 114 that the controller has selected for each of the undercarriage assemblies 30*a*, 30*b*.

After it is determined how much force should be applied to the idler wheel 36 based on the recoil response curve 112 or the appropriate recoil response curve 114, the controller 100 signals the control valve assembly 80 to either supply fluid to or drain fluid from one or both recoil assemblies 64 in order to move one or both rods 70 relative to its or their corresponding housings 68 in order to exert more force or less force, respectively, on the idler wheels 36 of one or both of the undercarriage assemblies 30*a*, 30*b*. During travel in the rearward direction 28, this additional force on the idler wheel 36 is a force that counteracts the effect of the force exerted on the idler wheel 36 by the drive wheel 34 during travel in the rearward direction 28. Accordingly, in the manner described above, the controller 100 controls operation of the control valve assembly 80 so as to increase fluid pressure in the hydraulic cylinder 66*a* and/or hydraulic cylinder 66*b* to exert more force on one or both of the idler wheels 36. This force is exerted on the idler wheels 36 in the forward direction 26 to counteract the force that the rear drive wheel 34 exerts on the idler wheels 36 during travel in the rearward direction 28.

INDUSTRIAL APPLICABILITY

The present invention allows for determining the appropriate force to be applied to the idler wheel 36 based on the direction of operation of a track-type work machine and applying the appropriate force to the idler wheel 36 to achieve a predetermined tension on the drive track 40. When the track-type work machine is traveling in the direction from the drive wheel 34 to the idler wheel 36, the appropriate force to the idler wheel 36 may be applied in a variable manner based on a recoil curve, such as curve 112. When the track-type work machine is traveling in the direction from the idler wheel 36 to the drive wheel 34, the appropriate force to the idler wheel 36 may be applied in a variable manner by, first, determining the pressure to the drive wheel to select an appropriate recoil curve, such as curve 114, then determining the idler position, and then using the determined idler position value to determined the appropriate force based on the selected recoil curve.

With respect to the excavator 10 of the exemplary embodiment, the controller 100 communicates with the control valve assembly 80, the pressure sensors 84, and the position sensors 86 in order to ensure that the recoil response of the excavator 10 complies with the appropriate recoil curves for that excavator 10 in a particular situation. The pressure sensors 84 sense the fluid pressure to both hydraulic motors 52*a*, 52*b* of the hydraulic system 50, and the values of the sensed fluid pressures are inputted to the controller 100. Similarly, the position sensors 86 sense the position of the rod 70 relative to its corresponding housing 68 for both of the undercarriage assemblies 30, and these position values are also inputted to the controller 100. The controller 100 utilizes these values in an algorithm contained within the memory device 104 of the controller 100. The algorithm within the memory device 104 includes therein various operating parameters, including a plurality of recoil response curves for when the excavator 10 is traveling in the rearward direction 28 that are dependent, at least in part, on the drawbar load and environmental conditions. Again, there is generally only one desired recoil response curve for an excavator 10 that is traveling in the frontward direction 26.

Accordingly, during travel in the forward direction 26, the algorithm includes a recoil response curve 112. During travel in the rearward direction 28, from the plurality of recoil response curves available in the algorithm, the controller 100 provides an appropriate recoil response curve 114 (with respect to each idler wheel 36 for each of the undercarriage assemblies 30*a*, 30*b*) based on the drive pressure that the pressure sensor 84 senses is going to both hydraulic drive motors 52*a*, 52*b*. This drive pressure is proportional to the force pulling on the idler wheel 36 when the excavator is traveling in the rearward direction 28. Thus, the controller 100 provides the appropriate recoil response curve 114 for each idler wheel 36 to compensate for that force pulling on the idler wheel 36 for each of the undercarriage assemblies 30*a*, 30*b*.

For both undercarriage assemblies 30*a*, 30*b*, the controller determines how much the idler wheel 36 is recoiled using the position sensors 86 that sense the position of the rods 70 relative to their corresponding housings 68 of both hydraulic cylinders 66*a*, 66*b*. Knowing how much the idler wheel 36 is recoiled of each undercarriage assembly 30*a*, 30*b*, the controller 100 compares that sensed position value of the idler wheel 36 with the recoil response curve 112 (when traveling in the forward direction 26) or 114 (when traveling in the rearward direction 28) for each undercarriage assembly 30*a*, 30*b*. As stated above, as an example, using the recoil response curves 112 and 114 shown in the graph of FIG. 4, if the idler wheel 36 recoil is around 20 mm, then the amount of force that is appropriate to be exerted on the idler wheel 36 is shown as X_f in FIG. 4 when traveling in the

forward direction **26** and is shown as X_r in FIG. **4** when traveling in the rearward direction **28**.

To achieve that appropriate force on the idler wheel **36**, the controller **100** outputs signals to the control valve assembly **80**. Upon receiving the output signal from the controller **100**, the control valve assembly **80** supplies fluid to or drains fluid from one or both hydraulic cylinders **66***a*, **66***b* to achieve that appropriate force.

In contrast to the currently available work machines, the present invention allows for a recoil response for both forward and rearward directions. By monitoring the system conditions, such as drive pressure, the present invention takes into account factors such as drawbar load and under-foot conditions in selecting the appropriate recoil response curve. This allows for appropriate tensioning of the track chain during work operation and travel, thereby resulting in extending the useful life of the machine. While the disclosed embodiment refers to an excavator, it should be understood that the present invention has wider application to various types of tracked vehicles.

Other aspects and features of the present invention can be obtained from a study of the drawings, the disclosure, and the appended claims.

What is claimed is:

1. A method of operating a track-type machine having a drive wheel and an idler, the method comprising:

operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine;

determining a direction of operation of the drive wheel;

sensing a pressure of fluid being used to operate the drive wheel;

determining a force to be applied to the idler based on the determined direction of operation of the drive wheel and, depending on the determined direction of operation, the sensed pressure of fluid being used to operate the drive wheel;

applying the force to the idler.

2. The method of claim **1**, wherein said determining a force includes selecting a recoil curve from a plurality of recoil curves based on the sensed pressure of fluid being used to operate the drive wheel and selecting the force to be applied based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve.

3. The method of claim **2**, wherein the direction of operation is in a direction from the idler toward the drive wheel.

4. The method of claim **1**, wherein said applying the force includes operating a valve assembly to control fluid pressure within an actuator associated with the idler.

5. The method of claim **1**, wherein said determining a force includes determining a first force when the drive wheel is operated in a direction from the drive wheel toward the idler and determining a second force differing from the first force when the drive wheel is operated in a direction from the idler toward the drive wheel.

6. The method of claim **1**, wherein the force applied to the idler is a function of a drawbar load of the machine.

7. A work machine, comprising:

a source of pressurized fluid;

a fluid reservoir;

a drive track;

an idler;

a drive wheel, the drive wheel being operable to advance the drive track around the drive wheel and the idler;

an actuator mechanically coupled to the idler, the actuator being operable to increase and decrease a force being applied to the idler;

a valve assembly operable to control fluid flow from the source of pressurized fluid to the actuator and from the actuator to the fluid reservoir;

a pressure sensor configured to sense the pressure of fluid being directed from the source of pressurized fluid to the drive wheel; and

a controller configured to operate the valve assembly to apply a force to the idler based on a direction of operation of the drive wheel and, depending on the determined direction of operation, the sensed pressure of fluid being directed to the drive wheel.

8. A The work machine of claim **7**, further including a position sensor configured to sense a position of the idler, and

wherein the controller is configured to operate the valve assembly to apply the force to the idler by selecting a recoil curve from a plurality of recoil curves based on the sensed pressure of fluid being directed to the drive wheel and by selecting the force to be applied to the idler based on a point on the selected recoil curve that corresponds to the sensed position of the idler on the selected recoil curve.

9. The work machine of claim **1**, wherein the drive wheel is operable to advance the drive track in a first direction that is associated with movement of the work machine in a direction from the drive wheel toward the idler and in a second opposing direction that is associated with movement of the work machine in a direction from the idler toward the drive wheel, and

wherein the controller is configured to operate the valve assembly to apply a first force when the drive wheel is operated in the first direction and a second force when the drive wheel is operated in the second direction, the first force differing from the second force.

10. The work machine of claim **7**, wherein the force applied to the idler is a function of a drawbar load of the machine.

11. A method of operating a track-type machine having a drive wheel at a first end of the track-type machine and an idler at a second end of the track-type machine, the method comprising:

operating a drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine, the drive wheel being operable in a first direction associated with movement of the track-type machine in a direction from the drive wheel toward the idler and in a second direction associated with movement of the track-type machine in a direction from the idler toward the drive wheel;

determining a force to be applied to the idler based on a direction of operation of the drive wheel and a sensed position of the idler when the drive wheel is operated in the first direction, and, when the drive wheel is operated in the second direction, based on a direction of operation of the drive wheel, a sensed pressure of fluid being used to operate the drive wheel, and a sensed position of the idler; and

applying the force to the idler.

12. A method of operating a track-type machine having a drive wheel and an idler, the method comprising:

operating the drive wheel to advance a drive track around the drive wheel and the idler thereby moving the track-type machine;

determining a direction of operation of the drive wheel;

determining an amount of recoil of the idler;

determining, when the drive wheel is operated in a first direction, a force to be applied to the idler based on the determined direction of operation of the drive wheel and the amount of recoil of the idler; and applying the force to the idler.

13. The method of claim 12, further including, when the drive wheel is operated in a second direction opposite the first direction, sensing a pressure of fluid being used to operate the drive wheel,

wherein said force to be applied is determined based on the determined direction of operation of the drive wheel, a sensed pressure of fluid being used to operate the drive wheel, and the amount of recoil of the idler.

14. The method of claim 12, wherein said determining the amount of recoil includes sensing a position of the idler.

15. The method of claim 12, wherein the force applied to the idler is a function of a drawbar load of the machine.

16. The method of claim 12, wherein said applying the force includes operating a valve assembly to control fluid pressure within an actuator associated with the idler.

17. A work machine, comprising:

a source of pressurized fluid;

a fluid reservoir;

a drive track;

an idler;

a drive wheel, the drive wheel being operable to advance the drive track around the drive wheel and the idler;

an actuator mechanically coupled to the idler, the actuator being operable to increase and decrease a force being applied to the idler;

a valve assembly operable to control fluid flow from the source of pressurized fluid to the actuator and from the actuator to the fluid reservoir; and

a controller configured to determine a direction of operation of the drive wheel and an amount of recoil of the idler, and to operate the valve assembly, when the drive wheel is operated in a first direction, to apply a force to the idler based on the determined direction of operation of the drive wheel and the amount of recoil of the idler.

18. The work machine of claim 17 further including a pressure sensor configured to sense the pressure of fluid being directed from the source of pressurized fluid to the drive wheel,

wherein, when the drive wheel is operated in a second direction opposite the first direction, said force to be applied is determined based on the determined direction of operation of the drive wheel, a sensed pressure of fluid being used to operate the drive wheel, and the amount of recoil of the idler.

19. The work machine of claim 17, further including a position sensor configured to sense a position of the idler,

wherein the controller determines the amount of recoil of the idler based on a sensed position of the idler.

20. The work machine of claim 17, wherein the force applied to the idler is a function of a drawbar load of the machine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,948,783 B2
DATED : September 27, 2005
INVENTOR(S) : Brian D. Hoff

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

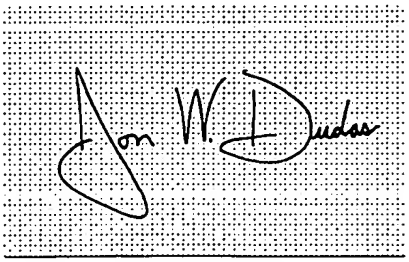
Column 13,
Line 37, after "operate the drive wheel;", insert -- and --.

Column 14,
Line 26, delete "claim 1," and insert -- claim 7, --.

Column 15,
Line 6, after "and" (second occurrence), the phrase "applying the force to the idler." should begin a new paragraph.

Signed and Sealed this

Seventeenth Day of January, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office